Neurology Asia 2011; 16(3) : 241 – 246

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis: A series of ten cases from a university hospital in Malaysia

Suhailah Abdullah *MBBS MMed*, Shen-Yang Lim *MD FRACP*, Khean Jin Goh *MBBS FRCP*, *Lucy CS Lum *MBBS MRCP*, Chong Tin Tan *MD FRCP*

*Division of Neurology, Department of Medicine and *Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.*

Abstract

Objective: To report on the incidence, and the clinical and laboratory features of patients seen at the University of Malaya Medical Centre with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.
Methods: The charts of all patients admitted to the adult neurology ward with encephalitis over an 18-month period from January 2010 to June 2011 were reviewed. Diagnosis of anti-NMDAR encephalitis was based on the presence of encephalitis plus antibody against the NMDAR. Two other paediatric patients with anti-NMDAR encephalitis seen over the same period were also included in this report.
Results: There was a total of 10 patients with anti-NMDAR encephalitis seen over the study period. The mean age was 18.1 years (range 9-29 years). Eight patients were female, two male. Five were Malay and five were Chinese. All patients had prominent psychiatric symptoms, followed by epileptic seizures. Nine patients had a movement disorder, orofacial dyskinesia being the commonest, and all had autonomic involvement. None had an underlying tumour. Treatments consisted of corticosteroid, plasma exchange and intravenous immunoglobulin (IVIG). The clinical outcome was variable, with full recovery (2), substantial recovery (3), partial recovery (4), and mortality (1) seen. Remarkably, the eight adult cases of anti-NMDAR encephalitis accounted for 50% of the 16 cases of encephalitis seen during the study period.
Conclusion: Anti-NMDAR encephalitis may be a relatively common cause of adult encephalitis among certain Asian groups. None of our cases was paraneoplastic in origin.

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-related encephalitis that was first recognised in 2005.[1] To date, around 400 patients with this disorder have been reported in the literature.[2] Although initially reported to occur mainly in young women with teratoma[3], it is now recognised to also occur in men and children (many of whom do not have an underlying tumour). The main clinical manifestations are psychosis, epileptic seizures, impaired consciousness, movement disorders, and autonomic dysfunction. Immune-based treatments have improved the clinical outcome in some patients.[2,4-6] This is a report of ten cases seen at the University of Malaya Medical Centre (UMMC) over 18 months from January 2010 to June 2011.

METHODS

The study was conducted at UMMC, Kuala Lumpur, Malaysia, a 1,200-bed hospital which serves as a community hospital to the surrounding area. As a tertiary referral centre, patients are also referred from the Klang Valley area and from elsewhere in Malaysia. The charts of all patients admitted to the adult Neuromedical service of UMMC from January 2010 to June 2011 with a diagnosis of encephalitis were reviewed. The diagnosis of anti-NMDAR encephalitis was based further on the presence of anti-NMDAR antibody. The antibody test was performed in the laboratory of Prof. Angela Vincent of the Institute of Immunology, Headington, Oxford, United Kingdom (UK).

Address correspondence to: Dr. Suhailah Abdullah, c/o Neurology Laboratory, University Malaya Medical Centre, 59100 Kuala Lumpur, Malaysia. Fax: 603-79494613, e-mail: suhailahabd08@yahoo.com

RESULTS

Over the study period, 16 adult patients in total were admitted to the adult Neuromedical service with a diagnosis of encephalitis. Of these, eight were positive for anti-NMDAR antibody and two were positive for *Streptococcus pneumoniae* from cerebrospinal fluid (CSF) culture. In the remaining six patients, no specific aetiologic / infective agent could be determined. Hence, anti-NMDAR encephalitis accounted for 50% of all encephalitis admissions to the adult Neuromedical ward over a period of 18 months. Seven cases were excluded from the study. Of these, five patients had tuberculous meningitis with hydrocephalus and impaired conscious level, and two patients initially diagnosed with encephalitis were found upon further investigation to have HIV-related space occupying lesions.

Two other paediatric patients with anti-NMDAR encephalitis were seen over the same period and their details are also included in this report, making a total of 10 patients. Their mean age was 18.1 years (range 9-29 years). Eight patients were female and two were male, five were Malay and five Chinese.

Clinical Features

Table 1 summarises the main clinical features, treatments and outcome of the ten patients with anti-NMDAR encephalitis. In three patients, there was a reported history of low-grade fever, without respiratory or gastrointestinal symptoms, prior to the onset of neuropsychiatric symptoms. However, none had a documented fever on initial presentation to our hospital.

Three patients (Patients 1, 5, 8) had a history of prior encephalitic illness of undetermined aetiology and presented during the study period with a relapse. The interval between initial symptom onset to the present illness ranged from 22 months to 10 years. All three patients had reduced cognitive function after the first illness, resulting in dropout from school.

All ten patients had prominent psychiatric symptoms as the initial manifestations, occurring over a period of 2-6 weeks. These included social withdrawal, agitation, and impulsive and aggressive behaviours (e.g., jumping out of window, hitting a newborn baby, behaving "like an animal"). Two patients reported tactile hallucinations described as "something crawling up" the limb or "wire tied around the arm". Two patients had auditory and visual hallucinations, requiring treatment with physical restraints and intravenous anti-psychotic drugs. One of the patients was initially admitted to the psychiatric ward with a diagnosis of acute psychosis. Seven patients needed anti-psychotic medication.

All ten patients developed epileptic seizures following the onset of psychiatric symptoms. Eight patients had focal seizures clinically, eight patients had generalised tonic clonic seizures, and four had status epilepticus. All patients required more than one anti-epileptic agent for seizure control.

Orofacial dyskinesia with chewing or kissing/ puckering movements of the lips was seen in nine patients. Three patients demonstrated abnormal posturing (dystonia) of the upper limbs that was eventually controlled with oral clonazepam or clobazam.

Autonomic involvement was seen in all patients. All patients had tachycardia (ranging from 100-124 beats per minute), five patients had hyperthermia (38-39.5°C), four had hypertension (systolic blood pressure 156-214 mm Hg, diastolic blood pressure 90-111 mm Hg), three had hyperventilation and two had hypoventilation. Four patients needed invasive ventilation for cerebral protection or because of haemodynamic instability.

All patients had cognitive impairment, eight with impaired conscious level. Two patients showed pyramidal signs. Two patients complained of sensory symptoms, but no objective sensory deficit was documented.

Investigations

All patients were negative for known causes of bacterial and viral encephalitis, as well as for serology for other autoimmune diseases. All patients had abnormal electroencephalography (EEG). The abnormalities consisted of excessive diffuse polymorphic slow waves in all patients, frontal sharp waves (3 patients), and asymmetrical alpha rhythm (2). Other results of investigations are summarised in Table 2. Three patients had a CSF lymphocytic pleocytosis with normal glucose and protein. Brain magnetic resonance imaging (MRI) was normal in eight patients. Patient 8 had mesial temporal sclerosis and Patient 9 had T2 hyperintensity of the left cerebral hemisphere gray and white matter. Computed tomography (CT) of the chest, abdomen and pelvis was performed in eight patients, which showed ovarian cyst(s) in two patients and thymic enlargement in one patient. Histological examination of the enlarged thymus revealed normal tissue. None of the patients had ovarian teratoma or other tumour.

Table 1: Summary of clinical features, treatments and outcome of patients with anti-NMDAR encephalitis.

Abbreviations. C = Chinese; F = Female; GTCS = Generalised tonic clonic seizure; IVIG = Intravenous immunoglobulin; M = Male or Malay; m = Months; y = Years; 2° = Secondary.

Case number/ Gender/Race/ Age/Duration of follow-up	Neuro-psychiatric symptoms	Movement disorder	Autonomic instability	Treatments	Outcome
1/F/C/16y/21m (initial presentation was at age 12y)	Social withdrawal, agitation, emotional lability, apraxia, echolalia, focal seizure with 2° generalisation/status epilepticus	Orofacial dyskinesia, bizarre gait	Tachycardia, hypertension, hypoventilation, hyperthermia	IVIG, IV methylprednisolone, oral prednisolone	Substantial recovery
2/F/C/21y/17m	Tactile, auditory & visual hallucinations, forgetfulness, agitation, focal seizure	Nil	Tachycardia, hypertension, hyperventilation	IV methylprednisolone, oral prednisolone	Full recovery
3/F/M/17y/4m (later lost to follow-up)	Social withdrawal, psychosis, focal seizure with 2° generalisation/ status epilepticus	Orofacial dyskinesia, upper limb dystonia/ athetosis	Tachycardia, hypertension, hypoventilation, hyperthermia, ileus	IV methylprednisolone, oral prednisolone, plasma exchange, IVIG	Partial recovery
4/F/M/24y/7m	Social withdrawal, aggression, psychosis, mutism, focal seizure with 2° generalisation	Orofacial dyskinesia	Tachycardia	IV methylprednisolone, oral prednisolone, plasma exchange	Substantial recovery
5/F/C/19y/7m (initial presentation was at age 12y)	Social withdrawal, inappropriate laughing, mutism, catatonia, GTCS	Orofacial dyskinesia	Tachycardia	IV methylprednisolone	Full recovery
6/F/M/14y/ 5 days	Social withdrawal, aggression, psychosis, GTCS	Orofacial dyskinesia, upper limb dystonia	Tachycardia, hyperthermia	Discharged against medical advice	Died at home
7/F/C/9y/6m	Social withdrawal, leg apraxia, aphasia, focal seizure with 2° generalisation	Orofacial dyskinesia, upper limb dystonia	Tachycardia, hyperthermia	IV methylprednisolone, IVIG, thymectomy	Partial recovery
8/F/C/24y /6m (initial presentation was at age 14y)	Social withdrawal, aphasia, focal seizure with 2° generalisation	Orofacial dyskinesia	Tachycardia, hyperthermia	IV methylprednisolone, plasma exchange	Partial recovery
9/M/M/9y/6m	Social withdrawal, leg apraxia, aphasia, right hemiparesis, focal seizure,	Orofacial dyskinesia	Tachycardia	IV methylprednisolone, IVIG	Partial recovery
10/M/M/29y/3m	Social withdrawal, aggression, psychosis, focal seizure with 2° generalisation	Orofacial dyskinesia	Tachycardia	IV methylprednisolone	Substantial recovery

Table 2: Investigation results of patients with anti-NMDAR encephalitis.

	n (%)
Cerebrospinal fluid	
White blood cell count	
Normal	7 (70%)
Pleocytosis	3 (30%) (range 8-12 lymphocytes/μL)
Protein	
Normal	10 (100%)
Glucose	
Normal	10 (100%)
Electroencephalogram	
Diffuse polymorphic delta waves	10 (100%)
Asymmetrical background	2 (20%)
Epileptiform discharges, frontal sharp waves	3 (30%)
Brain MRI	
Normal	8 (80%)
Bilateral mesial temporal sclerosis	1 (10%)
Left hemisphere T2 hyperintensity	1 (10%)
CT chest, abdomen & pelvis	
Tumour	0 (0)
Polycystic ovary	1 (12.5%)
Solitary ovarian cyst (< 1cm)	1 (12.5%)
Enlarged thymus gland	1 (12.5%)
Normal	5 (62.5%)

Treatment and Outcome

All patients were given general supportive treatment, and management for the seizures and abnormal movements. Four patients needed ventilatory support. Upon laboratory confirmation of the presence of anti-NMDAR antibody, all patents were given immunotherapy. IV methylprednisolone and/or oral prednisolone was given to all patients (except Patient 6, who self-discharged against medical advice), three patients had plasma exchange, and four patients were given intravenous immunoglobulin (IVIG). Thymectomy was performed in one patient with thymic enlargement.

As of last follow-up (this ranged from 5 days to 21 months), half the patients had good outcome with two patients experiencing full recovery and three patients having substantial recovery. Four patients made only a partial recovery and one patient died.

Example case report

Patient 1 is a 16-year-old Chinese girl who first presented to another hospital in December 2007 with status epilepticus, needing multiple anti-epileptic drugs and prolonged ventilation. Her condition was also complicated by autonomic instability. This was preceded by a three week history of abnormal behaviour, with tactile hallucinations ("something crawling up" her left hand and leg), fluctuating hand apraxia (inability to use chopsticks, tie shoelaces or play the piano), social withdrawal, mood lability and orofacial dyskinesia. CSF examination and brain MRI were normal. EEG repeatedly showed focal slowing over the left fronto-temporal region, intermixed with burst suppression. She was presumptively diagnosed with viral encephalitis and treated for this. She was eventually discharged from hospital in May 2008 on oral sodium valproate, levetiracetam, and clonazepam. At this time, she was able to carry out activities of daily living independently, but cognition was still impaired. By June 2008, there was further improvement in her cognitive and physical functions and she was able to solve 100-piece puzzles, perform simple calculations, and occasionally was able to write.

However, she again developed seizures in March 2009 when her anti-epileptic medication was stopped. Her cognitive function progressively deteriorated and by October 2009, her speech was limited, and involuntary orofacial movements and an abnormal bizarre gait (probably representing a disinhibitory behaviour) were seen. Brain MRI was again normal. In January 2010, there was further functional decline and she was able to answer simple questions only; she was unable to hold cutlery steadily, needed prompting to toilet and gait became more unsteady and shuffling. She also had more seizures. There were involuntary orofacial (chewing and kissing) movements.

Extensive investigations were done to look for the specific aetiology of her encephalitis, including screening for autoimmune diseases but these were all normal or negative. CSF analysis and brain MRI brain were again normal. EEG showed generalised slow waves. Based on her clinical picture, the anti-NMDAR antibody was tested and found to be positive. Body CT scan showed bilateral multiple ovarian cysts (the largest approximately 1 cm in diameter), but with no evidence of teratoma.

She was given a course of IVIG, followed by IV methylprednisolone and tapering dose of oral steroid. Over the subsequent months, there was a steady and impressive recovery. At her last clinic visit in January 2011, she had returned to school and was again able to read and write in Malay, English and Mandarin. She was able to do calculations in the range of thousands, sing her favorite pop song and attend music lessons. At this time, she was on sodium valproate and levetiracetam.

DISCUSSION

The diagnosis of anti-NMDAR encephalitis in our patients was based on the clinical features of encephalitis, absence of other causes of encephalitis, and the presence of anti-NMDAR antibody. Anti-NMDAR antibody has been found to be highly sensitive and specific (up to 100%) for anti-NMDAR encephalitis.[7] Furthermore, the clinical and laboratory features of our series of patients with anti-NMDAR encephalitis (predilection for affecting young adult females, prominent psychiatric manifestations, seizures, involuntary movements particularly orofacial dyskinesia, autonomic manifestations, relative absence of MRI abnormality, response to immune therapy, and relapsing disease) are consistent with previous reports.[2-6]

However, none of our patients had an associated ovarian teratoma or any other tumour, suggesting that these cases were non-paraneoplastic in origin. Although anti-NMDAR encephalitis was initially reported mainly among young women with teratoma[3], later series showed that a smaller proportion of cases (40-50%) was associated with an underlying tumour (less in children and men).[2,4-6] However, we cannot exclude the possibility that with longer follow-up, some of our patients may develop ovarian teratoma or another tumour.

Remarkably, our eight adult cases of anti-NMDAR encephalitis accounted for half of the adult hospital admissions for encephalitis over an 18-month study period. This suggests a high incidence of anti-NMDAR encephalitis in the Malaysian population. Awareness of anti-NMDAR encephalitis as an entity in the local medical community is low, and none of our patients was referred with a suspected diagnosis of this disorder, reducing the possibility of referral bias. One study showed that this disorder was responsible for 20% of encephalitis in a UK tertiary intensive care unit.[8] In contrast, another study from the UK reported that anti-NMDAR encephalitis accounted for only 4% of 203 acute encephalitis cases.[9] In a nation-wide survey from Japan, Kamei *et al*. estimated a relatively low annual incidence (0.33 per one million population) of "severe non-herpetic encephalitis of unknown etiology"; two-thirds of patients in this study who were tested were found to be positive for anti-NMDAR antibody (GluR ε2 or δ1 type).[10]

Our cases were of Malay and Chinese race (five patients from each group). Malaysia has a multi-ethnic population; the ethnic composition of patients admitted to UMMC in 2010 was 47% Malay, 27% Chinese, 21% Indian, and 5% others races. Most Malaysian Chinese are descendants of migrants originally from Southern China (provinces of Guangzhou, Fujian, and Hainan). Anti-NMDAR encephalitis may thus be relatively common among the Malay and Southern Chinese population. Interestingly, in their series of 44 patients with anti-NMDAR encephalitis from the UK and Europe, Irani *et al*. reported a high proportion (29%) of non-Caucasians.[4] In another series of ten cases of anti-NMDAR encephalitis from the United States, only two were white Hispanic; the others were Asian (3), Black (3), and Pacific Islander (2)[11], again suggesting that certain ethnic groups may be predisposed to this disorder.

In conclusion, anti-NMDAR encephalitis may be a relatively common cause of adult encephalitis among certain Asian groups. Although a search for underlying tumour is warranted in patients with this disorder, an increasing number of cases appear to be non-paraneoplastic in origin.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Prof. Wong Kum Thong and Miss Wing Su from the Department of Pathology, University of Malaya, for their assistance in acquiring the serum and arranging transportation of samples. We are also grateful to Prof. Angela Vincent (Institute of Immunology, Oxford, UK); the detection of anti-NMDAR antibody by her laboratory has enabled us to provide appropriate management to our patients.

REFERENCES

1. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Ann Neurol* 2005; 58:594-604.
2. Dalmau J, Lauwster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; 10(1):63-74.
3. Dalmau J, Tuzun E, Wu HY, *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; 61:25-36.
4. Irani SR, Bera K, Waters P, *et al*. N-Methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010; 133:1655-67.
5. Florance NR, Davis RL, Lam C, *et al*. Anti-N-Methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009; 66(1):11-8.
6. Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges. *Lancet Neurol* 2011; 10:759–72.
7. Wandinger KP, Saschenbrecker S, Stoecker W, Dalmau J. Anti-NMDA-receptor encephalitis: A severe, multistage, treatable disorder presenting with psychosis. *J Neuroimmunol* 2011; 231:86-91.
8. Davies G, Irani SR, Cordelia C, *et al*. Anti-N-methyl-D-aspartate receptor antibodies: A potentially treatable cause of encephalitis in the intensive care unit. *Critical Care Med* 2010; 38(2):679-82.
9. Granerod J, Ambrose HE, Davies NWS, *et al*. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective Study. *Lancet Infect Dis* 2010; 10:835-44.
10. Kamei S, Kuzuhara S, Ishihara M, *et al*. Nationwide survey of acute juvenile female non-herpetic encephalitis in Japan: relationship to anti-N-methyl-D-aspartate receptor encephalitis. *Internal Med* 2009; 48:673-9.
11. Gable MS, Gavali S, Radner A, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *Eur J Clin Microbiol Infect Dis* 2009; 28:1421-9.