REVIEW ARTICLE

Anti-N-methyl-D-aspartate receptor (NMDAR) Encephalitis in Malaysia: A Review Article

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ABSTRACT

N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is recognized as an autoimmune encephalitis, which is due to autoantibodies against synaptic NMDAR. This disorder affects individuals aged 23 months to 76 years and has a wide range of presentations. In Malaysia, more than 20 cases have been reported. Timely diagnosis and definitive immunotherapy are vital in optimizing functional recovery and prognosis. However, early diagnosis of the condition is often missed due to low awareness among clinicians in Malaysia. This article gathered the medical literature from Malaysia and highlights the aetio-pathophysiology, clinical presentation and management of the disease.

Keywords: Anti-NMDAR encephalitis, NMDAR antibody, Autoimmune, Encephalitis, Malaysia

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INTRODUCTION

N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is an autoimmune encephalitis where autoantibodies are produced against synaptic NMDAR. It is most commonly seen in young adults and children (1). It was first described in a young woman in the year 2007, who was later found to have ovarian teratomas (1). However, subsequent reports revealed that both genders, with or without tumours were equally affected (2,3). The presentations of the disease vary widely among individuals but psychiatric manifestations are commonly seen at the onset of illness (4). The diagnosis of the condition is often delayed and prognosis is poor due to the low awareness among clinicians in Malaysia. Clinicians should always maintain a high index of suspicion in view of the high mortality rate of the disease and the prognosis is good if it is treated early (5-6).

In this paper, we review a total of 12 studies concerning anti-NMDAR encephalitis cases in Malaysia pertaining to their clinical presentations, investigation results, treatment and outcome (Table I).

EPIDEMIOLOGY

A population-based prospective study suggests that anti-NMDAR encephalitis is one of the most common causes of autoimmune encephalitis(7). There are no published data on the prevalence rate of the disease globally. In Malaysia, more than 20 cases have been reported (5, 8–17).

This disorder affects individuals aged 23 months to 76 years(2,18,19). Studies report that 59% of cases are associated with ovarian teratomas(2) and most of the cases are found in the reproductive age group with a female-to-male ratio of 4:1(20). It is postulated that the sex hormones have an essential role in disease development because the gender difference was less prominent in the pediatric population (21,22).

AETIO-PATHOPHYSIOLOGY

As an ionotropic glutamate receptor, NMDAR is responsible for brain disorders such as Alzheimer's disease and Schizophrenia. Other substances like ketamine and phencyclidine (which are NMDAR antagonists) are associated with psychotic and dissociative experiences (23). Therefore, researchers suggest a few possibilities for the occurrence of NMDAR autoimmunity (24).

One of the hypotheses suggests that NMDAR encephalitis is an immune disorder due to the presence of oligoclonal bands, intrathecal synthesis, and pleocytosis in cerebrospinal fluid (CSF) (2). NMDAR encephalitis is known to be associated with ovarian teratoma (1). A likely mechanism is where the tumorous cells trigger

Table 1: Summary of Medical Literature Review of anti-N-Methyl-D-Aspartate Receptor Encephalitis Cases in Malaysia

No	Authors	Type of study (No of subjects)	Age (years) / Gender	Main clinical features (No of subjects)	Presence of anti-NMDAR antibody	MRI brain findings (No of subjects)	EEG findings (No of subjects)	Presence of tumour	Treatment (No of subjects)	Outcome (No of subjects)
1	Abdullah *et al.* (2011)[8]	Case Series (10)	9-29 / F: 8 M: 2	• Seizures (10) • Autonomic instability (10) • Orofacial dyskinesia (9) • Social withdrawal (9) • Psychosis (9) • Cognitive deficits (4) • Catatonic feature (3) • Upper limb dystonia (3) • Bizzare gait (1)	Serum	Normal (8) Bilateral MTS* (1) Lt hemisphere T2 hyperintensity (1)	Diffuse polymorphic delta waves (10) Asymmetrical background (2) Epileptiform discharges, frontal sharp waves (3)	No	IV Methylprednisolone (9) Oral Prednisolone (4) IVIG (4) PLEX (3) Thymectomy (1)	Partial recovery (4) Substantial recovery (3) Full recovery (2) Death (1)
2	Viswanathan TT, Cheong B. (2013)[12]	Case Report (1)	24 / M	• Psychosis • Seizures • Orofacial dyskinesia • Dystonia	Serum	T2/FLAIR hyperintensity at Lt hippocampus and medial temporal lobe	Generalized slow wave activity	No	IV Methylprednisolone IVIG PLEX	Death
3	Nadarajah R. (2015)[5]	Case Report (1)	35 / M	• Psychosis • Status epilepticus • Orofacial dyskinesia • Autonomic instability	Serum	Normal	Asymmetric diffuse attenuated background with slower frequency on the right with excessive beta activities	No	IV Methylprednisolone IVIG PLEX Antipsychotic ECT	Partial recovery
4	Abdullah *et al.* (2015)[31]	Retrospective (16)	7-29 / F: 11 M: 5	• Seizure (16) • Autonomic instability (16) • Withdrawn (15) • Orofacial dyskinesia (11) • Psychosis (9) • Aphasia (7) • Catatonic feature (5) • Cognitive deficits (3) • Upper limb dystonia (3) • Abnormal gait (1) • Lower limb dystonia (1) • Upper and lower limb dystonia (1)	Serum	Normal (14) Bilateral MTS (1) Rt hemisphere T2 hyperintensity	Prominent background slowing in delta-theta range (16) Asymmetric background: • Mild (4) • Marked (7) • No (5) Interictal spike (3)	Benign ovarian teratoma (2)	IV Methylprednisolone (16) Oral Prednisolone (11) IVIG (3) PLEX (2) Excision of tumour (2) Thymectomy (1)	Full (9) Substantial (5) Partial (1) Unknown (1)
5	Hafidz MI, Hung SK (2016)[11]	Case Report (1)	30 / F	• Psychosis • Headache • Dysarthria • Orofacial dyskinesia • Choreoathethosis • Involuntary movement	CSF	Normal	Lt Temporal slowness	No	IV Methylprednisolone IVIG PLEX IV Cyclophosphamide	Partial recovery
6	Low JM (2017)[9]	Case Report (1)	18 / M	• Withdrawn • Aggression • Psychosis • GTC seizure • Orofacial dyskinesia • Autonomic instability	CSF	Normal	Diffuse slowing of delta waves	No	IV Methylprednisolone IVIG	Death
7	Khoo *et al.* (2017) [17]	Case Report (1)	21 / F	• Bitemporal headache • Psychosis • Memory loss • Status epilepticus • Orofacial dyskinesia • Autonomic instability	Serum	High signal intensity and cortical thickening at medial aspects of bilateral temporal lobes	Diffuse slow delta waves in both hemispheres	Ovarian tumour	IVIG Excision of tumour	Disabled
8	Chaw *et al.* (2017)[13]	Case Report (1)	20 / F	• Seizures • Abnormal behaviour • Memory loss • Visual hallucination	Serum	Normal	Slow background activity	Ovarian teratoma	IV Methylprednisolone PLEX Excision of tumour	Substantial
9	Fauzi *et al.* (2017)[14]	Case Report (1)	21 / F	• Bizarre behaviour • Memory loss • Status epilepticus • Autonomic instability • Orofacial dyskinesia	CSF & serum	Enlarged Lt hippocampus with subtle T2 hyperintensity, extensive cortical and white matter changes and generalized cerebral atrophy with asymmetrical loss at temporal lobe, hydrocephalus	Diffuse slow delta wave activities without epileptiform discharge	Ovarian teratoma	IVIG Excision of tumour	Disabled

Table 1: Summary of Medical Literature Review of anti-N-Methyl-D-Aspartate Receptor Encephalitis Cases in Malaysia (*continued*)

No	Authors	Type of study (No of subjects)	Age (years) / Gender	Main clinical features (No of subjects)	Presence of anti-NMDAR antibody	MRI brain findings (No of subjects)	EEG findings (No of subjects)	Presence of tumour	Treatment (No of subjects)	Outcome (No of subjects)
10	Sivaroo-ban *et al.* (2018)[10]	Case Report (1)	16 / M	• Seizure • Psychosis • Orofacial dyski-nesia	CSF	Normal	Rt hemisphere cortical dys-function	No	IV Methylpred-nisolone Oral Prednis-olone IVIG Oral Azathio-prine Antipsychotic (Risperidone then changed to Olanzapine)	Unknown
11	Hung *et al.* (2019)[15]	Case Report (1)	44 / M	• Focal face and up-per limb twitching • Language disinte-gration • Abnormal be-haviour • Intractable seizure	CSF & serum	Normal	Partial epilepti-form activity at Lt fronto-central region with fast spread to Rt hemisphere	No	IV Methylpred-nisolone IVIG IV Cyclophos-phamide	Full
12	Sim *et al.* (2019)[16]	Case Report (1)	37 / F	• Treatment resistant psychosis • Cognitive deficits	Not done	Not done	Not done	Ovarian teratoma	Excision of tumour	Full

(*F*: Female; *M*: Male; *Lt*: Left; *Rt*: Right; *CSF*: Cerebrospinal fluid; *MRI*: Magnetic Resonance Imaging; *FLAIR*: Fluid-attenuated Inversion Recovery; *MTS*: Mesial Temporal Sclerosis; *EEG*: Electro-encephalogram; *IV*: Intravenous; *IVIG*: Intravenous Immunoglobulin; *PLEX*: Plasma Exchange; *ECT*: Electroconvulsive Therapy)

the expression of NMDAR leading to a cascade of autoimmune response(25). In one study, NMDAR antibodies are detected in all 25 ovarian teratomas excised from patients with anti-NMDAR encephalitis (25). In some reports, it is mentioned those tumours are only found in about a quarter (26%) of the cases (26). Dalmau et al. report that the presence of tumors and NMDARs auto-antibodies are titre-dependent (2). Patients with tumours produce higher titres of antibodies and result in a more prominent immune response than those with no tumours detected (27).

Children under the age of 18 are less likely to identify the tumours (6). Therefore, other possible mechanisms for triggering the disease need to be considered. Peery et al. suggest that the encephalitis could be triggered by infections (23). The autoantibodies development is caused by infectious agents that shared similar epitopes as NMDAR (23). One of the pathogens identified is Herpes Simplex Virus (HSV) (28-30). A study has described that patients presented with prodromal viral-like illness before the neurological manifestations(4). There is postulation that the damaged or infected NMDARs expressed tissues outside the nervous system resulting in host immune activation and subsequently loss of tolerance to the receptors (23).

CLINICAL PRESENTATION

The presentations of anti-NMDAR encephalitis are widely variable, thus making it difficult to accurately diagnose the condition. These clinical symptoms are divided into early, middle and late, which is usually associated with a prodrome, and eventually more overt physical symptoms, neurological and / or psychiatric manifestations (31).

Clinical presentations of anti-NMDAR encephalitis are summarized as below:

(a) A non-specific prodrome phase: patients can present non-specific symptoms including headache, fever, viral-like illness (respiratory or gastrointestinal symptoms) weeks before the more acute psychiatry manifestations (2).

(b) Psychiatric symptoms: anxiety, sleep disturbances, mood disturbances including depression or mania, mood lability, psychosis, agitation, catatonia and behavioral abnormalities(32). Behavioral problems commonly present early in the progression of this syndrome (32).

(c) Cognitive dysfunctions: such as amnesia, short term memory loss and difficulty in concentration (6).

(d) Motor dysfunction: patients often develop dyskinetic movements, including orofacial dyskinesias which may be presented at an early stage. This is an important clue to achieve the diagnosis (2).

(e) Autonomic instability: Disturbance in respiration and hemodynamic often result in intensive care unit management (2).

(f) Seizures are commonly associated with anti-NMDAR encephalitis. There are approximately half of the patients with anti-NMDAR encephalitis who have epileptiform discharges, which might present in early stage and often evolve into a generalized slow wave (2).

In Malaysia, most of the reported cases present with prominent psychiatric symptoms at early stage of disease followed by epileptic seizures (8-17). Some develop movement disorders, with orofacial dyskinesia being the most common, and almost all have autonomic involvement (8-17). The manifestations of anti-NMDAR encephalitis in the paediatric age group are more difficult to be recognized by clinicians as the symptoms are vaguer(3). Children suffering from this illness could present with both mood and behavioral changes (3). Mood changes that have been observed include agitation, irritability and temper tantrums while behavioral

changes seen are mostly disorganized and aggressive behavior (3). Evidence show that further course of the disease involved progressive speech deterioration followed by generalized stereotyped movements(3). These movements might be mistaken as epileptic in this population (3). Sleep problems especially insomnia is more commonly seen than hypersomnia in paediatric patients(26). Many of them also present with urinary incontinence(26). In addition, autonomic dysregulation like central hypoventilation is more common than in adult patients (66% in adults; 23% in children). The symptoms are less severe compared with those in adults(2,3).

DIAGNOSIS

The main diagnostic criteria for anti-NMDAR encephalitis is to detect the autoantibodies directed against NMDAR either from serology or CSF(33). CSF positivity is considered necessary and sufficient for a definitive diagnosis(33). Majority of the cases reported in Malaysia have positive CSF serology for anti-NMDAR antibody. Thus, easy accessibility to a reliable diagnostic test is very important to confirm clinical suspicion. However, in Malaysia, this service is not widely available. Only a few centers are providing the service of detecting anti-NMDAR antibody in CSF and/or serum, such as Institute Medical Research Central and private laboratory service (e.g. Lablink). Nevertheless, in the context of Malaysia, any clinician should always bear in mind the presence of other antibodies that was directed towards other antigens such as LGI1, CASPR2, AMPAR, GABAAR, GABABR, Hu, Ma2, CRMP5, Amphiphysin, D2R, DPPX, MgluR5, IgLON5, Neurexin3α, ARHGAP26, Synapsin, AK5, and GFAP in cases where NMDAR is negative in either CSF or serum (20,31). Other laboratory workups aim to exclude other differential diagnoses such as viral or bacterial encephalitis(20,31). Raised level of proteins and pleocytosis or detection of oligoclonal bands are found during analyses of CSF(20). These findings represent about 60–70% of the cases(20,31). These tests are not popular among local clinicians due to low awareness and limited resources. Magnetic resonance imaging (MRI) of the brain does not show abnormality in 70% of cases(33). However, hyperintensities have been detected in areas including the hippocampi, cerebellum, cerebral cortex, basal ganglia, brain stem, frontobasal and insular regions in about one-third of the cases (1). In Malaysia, 80% of the cases have normal MRI brain. According to a case series done by Abdullah et al, one patient had mesial temporal sclerosis and another patient had T2 hyperintensity of the left cerebral hemisphere gray and white matter.(8) Other abnormal findings of MRI brain that have been observed in Malaysia include hyperintensity of the left hippocampus and medial temporal lobe in the T2/FLAIR sequence (12). One case report found extensive cortical and white matter changes and generalized cerebral atrophy with asymmetrical loss at the temporal lobes when a follow-up MRI brain was performed 13 weeks after admission (14). Abdullah et al. from University Malaya Medical Centre has reviewed 99 electroencephalograms (EEGs) from 16 patients with anti-NMDAR encephalitis (15). From this study, the EEGs performed during the psychiatric and cognitive functions impairment phase showed diffuse background slowing in delta-theta range, and the frequency improved with improvement in cognitive status (34).

Herken et al. classified these clinical constellations to 'yellow flag' and 'red flag' to aid clinicians to make a prompt diagnosis (31). Clinicians should consider the presence of these 'yellow flag' an autoimmune in origin i.e. autoimmune encephalitis. The presence of 'red flag' should prompt the investigation for anti-neuronal autoantibodies in psychiatric patients (31). The 'yellow flag' signs include impaired consciousness and other neurological deficits that affect postures or movements and autonomic stability (31). Focal neurological deficits like aphasia or dysarthria is also categorized under 'yellow flag' signs (31). Some of the cases also present with progressively worsening of first episode psychosis and catatonia (31). Electrolyte imbalance e.g. hyponatraemia and presence of headaches are considered as 'yellow flag' symptoms (31). Clinical 'red flag' signs are seizure, facio-brachial dystonia and suspected malignant neuroleptic syndrome. 'Red flag' laboratory findings are CSF abnormalities such as lymphocytic pleocytosis or positive detection of specific oligoclonal bands, MRI imaging that shows mesial temporal hyperintensities and atrophy as well as slowing, epileptic activity or extreme delta brush on EEG readings (31).

DIFFERENTIAL DIAGNOSIS

Patients with anti-NMDAR encephalitis usually present to either neurologists or psychiatrists first depending on which symptoms occur on initial presentations.

Neurological

In Malaysia, viral and bacterial meningoencephalitis are the most common differential diagnosis for patients who first present with neurological symptoms accompanied by a prodromal phase of flu-like illness(8–10, 12-17). This is seen in almost all the cases reported locally (8–10, 12-17). Other neurological differential diagnoses would be cerebral vasculitis or other forms of autoimmune encephalitis and encephalitis lethargica(35). Review of Malaysia literature shows that majority of the cases present with seizure and dyskinetic movements (8–10, 12-17). Seizure activities can often be mistaken for dyskinetic movements and vice versa(36). High index of suspicion is recommended when examining these movements(36).

Psychiatric

New-onset psychosis is not uncommon in patients with anti-NMDAR encephalitis (37). Many of them

are misdiagnosed as having Brief Psychotic Disorder and Catatonia (37). It is estimated that 5-10% of first-onset psychosis are caused by this disorder (37,38). Neuroleptic malignant syndrome is frequently considered a differential diagnosis, especially in cases where antipsychotic medications are prescribed, and they are found to be febrile with rigidity (6). This might post a great challenge in both diagnostic and management process.

TREATMENT OPTIONS

The treatment of anti-NMDAR encephalitis should involve a multi-disciplinary approach and usually requires a long-term rehabilitation (20). The principle of treatment is to aim at the underlying cause and the complications that arise from the encephalitis i.e. the mood irregularities, abnormal behavior and psychotic symptoms (20). As mentioned above, symptoms of anti-NMDAR encephalitis are observed to be antibody titer-dependent (27). Patients with no detection of tumour tend to recover much more gradually than those with tumour identified. There are reports of tumours found in patients several years after the initial onset of anti-NMDAR encephalitis (3). It is postulated that MRI and PET scan could not pick up slow-growing occult tumours, thus the delay in detection (3). Therefore, annual pelvic MRI screening is recommended for anti-NMDAR patients without tumour (3).

Based on the previous studies done in Malaysia, almost all cases are treated with immunotherapy (8-17). Usually the treatments' regime consists of corticosteroid and intravenous immunoglobulin (IVIG) (8-17). Plasma exchange would commence when patients show poor response to intravenous corticosteroid and immunoglobulin (8-17). The clinical outcome is variable. In a case series, out of 10 patients, 2 achieved full recoveries, 3 substantial recoveries, 4 partial recoveries, and 1 mortality (8). Similarly, for other individual case reports, 4 out of 7 made full recoveries while others succumbed to the condition (9-13). For treatment of psychiatric symptoms, antipsychotics have been used in all the cases with delusions, hallucinations and disorganized behavior (20). Antipsychotics must be used with caution because they may complicate the clinical picture by triggering neuroleptic malignant syndrome (20). There is no recommendation on any particular antipsychotic to be used for treatment of psychiatric symptoms but options with minimal risk for extrapyramidal symptoms are preferred (39). In extreme cases of agitation, medical coma can be induced using phenobarbital and fentanyl (27). Clonidine, trazodone, and benzodiazepines have been used to regulate sleep-cycle (40). For mood dysregulation, common mood stabilizers like valproic acid and lithium have shown minimal benefit (27). Some clinicians suggest that regular benzodiazepines are necessary in relieving catatonia (41,42). In cases where patients fail to respond to optimal dose of benzodiazepines, ECT is recommended in controlling symptoms more effectively (43). All supportive measures should be tapered off once patient achieve remission with immunotherapy (44). There is no evidence to support that autoimmune psychosis relapse can be prevented by using antipsychotics maintenance treatment (44).

PROGNOSIS

Patients with anti-NMDAR encephalitis require a long-term rehabilitation for complete recovery and this causes prolonged hospital stay (44). The prognosis is related to the duration of illness and how early the treatment commenced (44). Studies show that patients who received early immunotherapy have better rates of recovery with fewer relapses (2). Relapses are reported in 15%–25% of the cases(17,33). It has been observed that patients without identifiable tumours or with relapsing teratomas would have more relapses and incomplete recovery (20,35). About a quarter of patients experience persistent, severe deficits or succumbed to the condition. In a series of ten cases reported in Malaysia, two patients achieved full recovery whereby three achieved substantial recovery, four attained partial recoveries and one died (8). In a study involving children and adolescents, about one-third of the cases achieved full recovery and half of the cases experienced significant improvement, but with mild functional impairments; and 8 out of 31 experienced very minimal disease advancement with signs of severe deficits (3). Other factors that predict better outcome including symptoms with less severity, admissions to intensive care unit, the timing of immunotherapy commencement and excision of tumour in cases where teratoma is detected (22). Clinicians have to remain vigilant for recurrence of psychotic symptoms as post-encephalitic patients are at risk of de novo psychotic disorder (43).

CONCLUSION

Anti-NMDA receptor encephalitis, despite many unanswered questions regarding the disease is indisputably a treatable cause of psychiatric symptoms in both adults and children if it is diagnosed early. The awareness among clinicians in Malaysia regarding this condition are relatively low and often leads to delay in diagnosis and treatment (8). Hence, it is important for front liners in primary care and emergency department to work hand-in-hand with psychiatrists and neurologists to be equipped with knowledge in this disease, thus facilitating early screening and diagnosis.

Timely diagnosis and definitive immunotherapy are vital in optimizing functional recovery and prognosis (29). To date, as there are limited centers providing tests to detect anti-NMDAR antibody in CSF and serology in Malaysia, diagnosis and treatment are frequently delayed. Other than preparing more widely available facilities to aid

diagnosis, clinicians should always have a high index of suspicion when patients present with characteristic clinical syndrome.

More research is needed to illuminate the optimal treatment for this disease. The best clinical outcomes could be achieved through multidisciplinary approaches.

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