Anti N-Methyl-D-Aspartate receptor encephalitis: An under-recognised cause of encephalitis

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SUMMARY

Anti-N-Methyl-D-Aspartate receptor (NMDAR) encephalitis is an immune mediated condition with characteristic clinical presentation. We report the first case from Borneo, Sabah and the use of electroconvulsive therapy (ECT) in treating recalcitrant psychiatrist symptoms associated with this condition.

INTRODUCTION

Anti-N-Methyl-D-Aspartate receptor (NMDAR) encephalitis is an under-recognized cause of encephalitis in Malaysia, despite one centre reporting up to half adult hospital admission for encephalitis during the 18 months study period was due this condition.[1] The main reasons contributing to under diagnosis of this condition is the lack of awareness among doctors and difficulties in performing antibody testing except in reference laboratories. First described in 2005,[2] it was initially proposed as immune encephalitis in young women associated with ovarian teratoma.[3] We report the first case of anti-NMDAR encephalitis in Borneo, Sabah in a young man with no associated tumour.

CASE REPORT

35-year-old Kadazan gentleman with no known medical illness presented with a 2-week history of new onset of behaviour change. He was noted to be more reclusive and having insomnia progressing to an agitated, disinhibited and aggressive behaviour in which in which he assaulted a family member. He had to be restrained by the police before being admitted to the psychiatry hospital where he was treated for an acute psychotic episode.

Five days into admission he developed an episode of generalised tonic-clonic seizure and was transferred to our tertiary care centre. Neurological examination noted fluctuating level of consciousness with loss of ability to speak and make eye contact. He was agitated and it was noted he had self-harming behaviour (biting lips and knocking arms and legs on the bed). Pupils were equal and reactive, corneal, oculocephalic, cough and gag response was intact. Vestibular-oculocephalic test was not performed. There was voluntary stiffness of the neck. Limb examination revealed normal tone; power could not be accessed objectively. Reflexes were symmetrically present in both upper and lower limbs. Babinski and Hoffman sign was negative. Cerebellar examination and fundoscopy could not be performed, as the patient was uncooperative. Other systemic examination was unremarkable. In the ward, the patient developed status epilepticus needing intubation and ICU care where he required multiple high doses of anti-convulsant drugs and general anaesthesia to control his seizures.

Extensive investigations for metabolic, infectious, toxic, autoimmune, central nervous system and psychiatric disorders were performed, summarised in table I. Brain computed tomography was normal and MRI reported a lacunar infarct in the left corona radiate, which was likely an incidental finding. There were no MRI changes in the temporal lobes. Electroencephalography (EEG) while on sedation showed asymmetric diffuse attenuated background, with slower frequency on the right, with excessive beta activities.

He was empirically treated for meningoencephalitis with acyclovir and ceftriaxone for 2 weeks. Although he was successfully extubated after 5 days his behavioural and psychiatric symptoms persisted and now was also noted to have orofacial dyskinesia. The first antibody test sent for NMDAR came back after 3 weeks negative. However, a diagnosis of possible anti-NMDAR encephalitis was made based on the typical clinical presentation of psychosis, orofacial dyskinesia and seizures, and lack of evidences suggestive of infectious origin. Concurrently a repeat serum sample of antibody to NMDAR was sent to a separate reference laboratory came back positive 2 weeks later. He was treated with a methylprednisolone and thereafter a course of plasma exchange for 5 cycles and intravenous immunoglobulin G. Computed tomography of the thorax-abdomen and pelvis, ultrasound of the testis and tumour marker panel screening was negative for tumours.

Despite improvement in the control of seizures, his behavioural symptoms did not resolve with immunotherapy needing antipsychotics and multiple courses electroconvulsive therapy (ECT). He was maintained with high-dose oral prednisolone (1mg/kg) with slow tapering, while on psychiatric treatment. He was discharged 4 months later, without any anticonvulsant or antipsychotic medication. At 9 months follow-up, he was able to perform activities of daily living and had improved social interaction; however he did not attain full premorbid functional status.

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Table I: Type of biopsy reports obtained with semi-automated and automated core needles

Laboratory parameters	Results
Hemoglobin (g/dL) (females 12.0-16.0, males 13.5-17.5)	15.7
TWBC, x 10^3 cells/ml (4.5-11.0)	11.6
Platelet count, x 10^3 cells/ µL (150-450)	473
Serum creatinine, mmol/L (63-133)	132
Serum urea, mmol/L (1.0-8.3)	10.2
Total serum bilirubin, mmol/L (<7)	8
Serum aspartate aminotrasferase, U/L (<37)	56
Serum alanine aminotransferase, U/L (<40)	76
Serum albumin, g/L (35-60)	53
Random plasma glucose, mmol/L	7.1
Serum Magnesium, mmol/L (0.53- 1.11)	1.20
Serum Inorganic phosphate, mmol/L (0.78-1.65)	1.46
Serum Corrected calcium, mmol/L (2.18-2.60)	2.48
Serum Sodium, mmol/L (132-146)	138
Serum Potassium, mmol/L (3.5-5.5)	4.1
Serum Chloride,, mmol/L (98-107)	101
C-Reactive Protein, mg/dL (0-0.30)	3.8
Erythrocyte Sedimentation Rate (ESR), mm/Hr	72
CSF opening pressure	14cmH_2O
CSF FEME	Blood stained. Not suitable for FEME analysis.
Total Red Blood Cells, cells/mm^3	--
Total White Blood Cells, cell/mm^3	--
CSF glucose, mmol/L (2.3-4.1)	4.2
CSF/serum glucose ratio (> 0.5)	0.59
CSF protein, g/L (0.15-0.45)	0.82
CSF gram stain	No organism seen
CSF Torula stain	No yeast cell seen
CSF EV71 PCR	Negative
CSF JE IgM	Non reactive
Hepatitis C virus Antibody (anti—HCV)	Non reactive
HIV Antigen	Non reactive
Hepatitis B Surface Antigen (HBsAg)	Non reactive
Rapid Plasma Reagin (RPR)	Non reactive
Blood culture	No Growth
Serum Anti Nuclear Antibody (ANA)	Negative
C3, g/L (0.90-2.07)	1.71
C4, g/L (0.17-0.52)	0.39
Serum Antithyroglobulin (ATG) (<1:100)	Non reactive
Serum Ceruloplasmin, g/L (0.22-0.58)	0.53
24- Hour Urinary Copper, µmol/L (0.00-0.90)	0.66
Thyroid function test Thyroid stimulating Hormone (TSH)	0.843

DISCUSSION

The diagnosis in our patient was made based on the characteristic clinical syndrome a positive NMDAR antibody. Although initially proposed as immune encephalitis among young women associated with ovarian tumors,[2,3] our patient being male and extensive investigation not revealing any tumours is in keeping with later series on this condition.[3] Distinguishing anti- NMDAR encephalitis from other form of encephalitis can be difficult, hence attention has to focus to a detailed history taking and keeping a high index of suspicion in patients presenting with encephalitis with associated psychiatric and autonomic manifestation especially patient in the younger age group. Antibody testing for CSF and serum is highly sensitive and specific [3] to this condition and can be now performed at reference laboratory locally. Although initial serum NMDAR antibody test done was negative, the consistent clinical findings and high index of suspicions led to a repeat testing and eventually the conformation of the diagnosis.

To date there has been no randomized controlled trials on the management of this encephalitis. Authorities propose concurrent treatment with methlyprednisolone and plasma exchange/immunoglobulin and removal of tumour if present and second line therapy with rituximab and cyclophsophomide for patients who fail to respond to first line treatment.[3] Good outcome can be expected early diagnosis and prompt management of these patients.[3] In our patient it was noted that he had persistence of behavioural and psychiatric symptoms despite showing good seizure control after the course of immunotherapy. This could possibly be attributed in the delay in diagnosis and receiving treatment, as there was no evidence of tumour noted to explain lack of response to treatment. Electroconvulsive therapy (ECT) has been used for control of psychiatric manifestation of patients with anti-NMDAR encephalitis [4] and in our patient this intervention was used to control the recalcitrant psychiatric symptoms with success. Previous case reports using this strategy have reported limited success in-patient where no tumour is found. The mechanism of ECT in anti-NMDAR-encephalitis in adults is poorly understood. Proposed theory in animal models includes modulation of glutamatergic synapses by ECT.[5] This treatment strategy has to be to further evaluated and validated by larger studies.

In summary anti-NMDAR encephalitis is still an under-recognized cause of encephalitis in Malaysia due to limitation that has been elucidated. Early diagnosis, treatment and removal of tumour if present will improve outcome of patients.

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