Anti NMDA Receptor Encephalitis: A Differential Diagnosis in a Young Patient Presenting with Neuropsychiatric Symptoms

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INTRODUCTION

Anti N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune encephalitis. NMDA receptors are ligand-gated cation channels that play a role in synaptic transmission and are highly expressed in the forebrain, limbic system and hypothalamus. This form of antibody mediated encephalitis is more common in women[1]. It is often misdiagnosed as viral encephalitis, neuroleptic malignant syndrome or acute psychotic disorder. Treatment is specific and delays are associated with a poorer outcome.

CASE REPORT

A 24 year old orang asli man was referred for fever, headache and vomiting for one week. He was noted to be confused initially. He did not have diarrhea or respiratory complains. He was a smoker but denied taking alcohol or recreational drugs.

Upon arrival, he was febrile but alert and orientated. He had no neck stiffness and neurological examination was normal. Other systems were unremarkable. The provisional diagnosis was meningo-encephalitis and he was started on IV Ceftriaxone and Acyclovir. Lumbar puncture was done and cerebro-spinal fluid (CSF) showed marked lymphocytic pleocytosis (1140 cells/ul). CSF protein was mildly elevated (531 mg/l) with normal glucose (CSF 3.9 mmol/l, RBS 6.2 mmol/l). No bacteria or fungus was isolated. The CSF was also negative for herpes simplex, varicella zoster, enterovirus, dengue virus and Japanese B encephalitis virus. Cryptococcal antigen was not detected. No malarial parasites were detected on blood films and patient was negative for HIV antibodies. Anti-nuclear antibodies were also negative.

Five days later, the patient developed psychotic symptoms like confusion, restlessness, incoherent speech and visual hallucination. He had generalized stiffness and abnormal oro-facial twitching. He subsequently developed intractable seizures and had to be ventilated. Seizures were difficult to control despite being on multiple anti-epileptics and continuous thiopentone infusion. MRI of the brain showed hyperintensity of the left hippocampus and medial temporal lobe in the T2/FLAIR sequence (figure 1). EEG showed generalized slow wave activity suggestive of encephalopathy.

The diagnosis of anti NMDA receptor encephalitis was suspected and later confirmed by detecting the antibodies in the serum. By this time, the patient had already been started on IV Immunoglobulin 0.4 g/kg/day for five days. IV Methylprednisolone 1 g daily was later added. The patient's condition did not improve and plasma exchange was planned. Unfortunately the patient developed nosocomial septicemia with acute renal failure and subsequently passed away. Although we were not able to perform a CT scan to look for occult malignancy, clinically the patient had no evidence of malignancy and tumor markers like β-HCG, CEA, CA125 and α-fetoprotein were negative.

DISCUSSION

Anti NMDA receptor encephalitis is associated with tumors in 60% of cases, usually ovarian teratomas or testicular tumors[2]. The mean age of patients is 23 years old but it is increasingly being recognized in adolescents and children[2]. It usually presents initially with a prodromal phase of fever, diarrhea or flu-like symptoms followed by a psychotic phase with personality and behavioural changes, irritability, anxiety, aggressiveness, delusions and paranoia. Patients will typically have dystonia and oro-facial dyskinesia during this phase. Seizures and autonomic dysfunction are common features. CSF and MRI brain findings are similar to the case described above.

Prompt treatment has been found to improve outcome. IV Immunoglobulin combined with Methylprednisolone is used as first line treatment. Alternatively, plasmapheresis can be used. If there is no clinical improvement, Rituximab and Cyclophosphamide should be considered. Second line treatment with rituximab and/or cyclophosphamide significantly improves outcome compared with no treatment or repeating 1st line therapy (56% vs. 27%, p=0.006)[3]. Patients who respond will require immune-suppression with Azathioprine, Mycophenolate or monthly Cyclophosphamide for up to a year. 75% of patients have full or substantial recovery but this may take up to 2 years[3]. Prolonged hospital stay is to be expected with reported median hospitalization of up to 2.5 months (range 2 to 14 months) [4]. Tumors should be actively searched for and if detected, resected as soon as possible. Relapses occur in 14% of cases[3]. Common causes of death in patients are infections,

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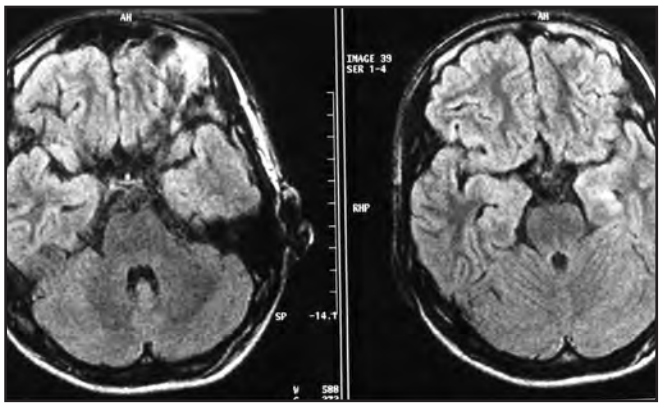

Fig. 1 : MRI of the brain showing hyperintensity of the left hippocampus and medial temporal lobe in the T2/FLAIR sequence.

acute respiratory distress syndrome, status epilepticus, sudden cardiac arrest and tumor progression.

Retrospectively, our case presented with rather classical clinical and investigation findings. As this diagnosis is rarely made outside of neurology referral centers, a high index of suspicion is required to ensure that this diagnosis is not missed and appropriate treatment instituted without delay.

CONCLUSION

Anti NMDA receptor encephalitis is a form of autoimmune encephalitis and is often misdiagnosed. It is commonly associated with tumors. Diagnosis can be confirmed by detecting the NMDA receptor antibody in patient's serum or CSF. Management is by early immune-suppression and resection of tumors.

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