CASE REPORT

Anti-NMDA Receptor Encephalitis Tricks Everyone: A Diagnostic Challenge

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Abstract

Anti-NMDAR encephalitis is second most commonest encephalitis after acute demyelinating encephalitis. It has been under recognised in our practice and the clinical presentation which may vary, poses a diagnostic challenge to the clinicians, especially to psychiatrists due to the prominent neuropsychiatric manifestation encompassing the disorder. This is a report of 2 cases of Anti-NMDAR encephalitis diagnosed in psychiatry ward who presented with prominent neuropsychiatric sign and symptoms. The male patient had prodromal viral flu like illness, aggressive and disorganised behaviour with visual hallucination and persecutory delusion for 2 days and subsequently developed abnormal movements. On the other hand, the lady presented with difficulties sleeping, auditory hallucinations and disorganised behaviour for 5 days. CT brain of both the patients were unrevealing. EEG was abnormal and NMDAR antibodies was detected in their CSF. The female patient had ovarian teratoma and she underwent surgical resection. Immunotherapy was initiated for both the patients. It is important to keep NMDAR encephalitis as a differential in patients presenting with acute psychiatric symptoms, poorly formed delusions, behaviour changes, abnormal movements and seizures. Early diagnosis, immediate immunotherapy and removal of the culprit malignancy is important for a better prognosis with up to 75% of patients achieving full recovery.

Keywords: Anti-NMDAR Encephalitis, Atypical Psychotic Symptoms, Ovarian Teratoma, Immunotherapy

Introduction

Anti-NMDAR encephalitis has been under recognised in our practice and diagnosing it has been a great challenge. The prominent neuropsychiatric presentation causes the patient to initially be treated in a psychiatric facility. Early diagnosis and prompt management is crucial as recovery is observed in more than 75% of all patients [1, 2]. Misdiagnosis by physicians tends to happen as initial signs of this illness mimics acute psychosis [3]. This disorder is the second most common cause of autoimmune encephalitis after acute demyelinating encephalomyelitis [4, 5]. It was first

described in the year 1997, in two different reports of young women who presented with ovarian teratoma and neuropsychiatric manifestation [6, 7]. Subsequently, case series in the year 2005, reported four young women with ovarian teratoma who displayed prominent psychiatric symptoms, memory loss, decrease level of consciousness, and central hypoventilation [2, 8, 9]. Ever since then, it has been seen in patients with varying ages, but commonly among the young adult and children with or without teratoma [10, 11]. The associated target antigen was then discovered in 2007 by Dalmau et all [10] as the NMDA receptor (NMDAR). NMDAR is a kind of glutamate receptor that contributes to memory and learning through the signal transmission in the central nervous system and antibody against the receptor causes the encephalitis [3]. We will be describing two cases, a male and a female patient with NMDAR encephalitis who presented differently and the dilemma of diagnosis that we faced.

Case 1

A 35 years old Chinese man with no significant of past medical history was brought to the Emergency Department for aggressive behaviour, persecutory delusion and visual hallucination for two days. He has no reported history of substance usage. He had low grade fever with no meningeal sign or neurological deficits. He was admitted to medical ward and acyclovir started as given concern for viral encephalitis.

Vital signs were within normal range. Laboratory studies and urine toxicology revealed no any profound metabolic or toxic disturbance. Brain computerized tomography (CT) were normal. CSF showed mildly elevated protein. He was not responsive to the anti-viral medications.

He continued to display psychotic behaviours in the ward. He was agitated and disorganised. He was referred to psychiatry team and the impression was revised to brief psychotic disorder. There was no improvement even after initiation of anti psychotics.

Subsequently, he developed two episodes of abnormal movement, repetitive, brief, rapid irregular involuntary movement that started with his upper limbs moving to the lower limbs lasting more than 30minutes followed by continuous slow writhing movement of lower limbs. It was treated initially as generalised tonic clonic seizures. EEG showed generalized but asymmetry with left more prominent show, intermittent alpha rhythm seen and no spike seen.

At this juncture, CSF autoimmune antibody serologies were sent and Anti-NMDA-R antibodies were detected. Hence immunomodulation therapy was started. Within two weeks his clinical state was gradually improved and discharged home well without any additional needs.

Case 2

This is 34 year old married Chinese lady with 2 children, with no known medical or psychiatric illness from middle socioeconomic class, working as a primary school teacher presented with acute onset abnormal behaviour for 5 days. She complained of difficulty in initiating sleep, feeling fearful that someone might harm her. She also believed that she possessed special powers of being able to predict the future after reading few paged of the Bible.

Her family members mentioned that patient also complained that she could hear voices asking her to choose between her safety and the safety of her husband and mother. They

notices that patient was talking incoherently and acting very strangely. There was an episode where she started crawling like a caterpillar with her 1 year old toddler in the hall and kept asking the husband to jump into the rainbow outside their house in order to save himself.

There was no history of her thoughts being known by others, expressing pervasive sadness or suicidal ideation. There was also no history of fever, headache, vomiting, substance abuse, seizures, head injury, loss of consciousness, recent travel history, sick contacts or ingestion of new food or medications. She had no family history of psychiatric illness and she pre-morbidly was functioning very well.

In the emergency department, her vital signs were within the normal limits. A detailed neurological examination revealed normal power and tone of muscles as well as Babinski reflex and no signs of meningeal irritation. Laboratory studies and urine toxicology did not reveal any profound metabolic or toxic derangement. Urgent plain CT brain was done and there was no intracranial pathology. She was noted to be speaking and mumbling incoherently. She was then admitted to inpatient psychiatric ward for acute psychosis and treated as Brief Psychotic Disorder.

Throughout her 6 days of admission in the psychiatric ward, her condition seemed to deteriorate despite optimisation of antipsychotics. She became non verbal, had episodes of blank staring for 15-20minutes and exhibited negativism. She also didn't tolerate orally and supportive care in the form of intravenous fluids were provided for patient. Upon referral to our medical liaison counterpart, an exhaustive biological check up was conducted to rule put possible organic cause. During the period of work up, she became febrile, her GCS dropped to E4V2M4, with frequent dyskinesia and desaturation therefore, she required intubation. Contract enhanced CT Brain revealed leptomeningeal enhancement. Lumbar puncture yielded clear cerebrospinal fluid (CSF), and negative CSF microscopy, culture, cytology and infection screen. Anti-NMDAR antibodies were detected in the patient's CSF. Intravenous methylprednisolone was given to the patient for 5 days. Her EEG revealed slowing of waves suggestive of moderate to severe encephalopathy. CT Thorax, Abdomen and Pelvis was done in view to look for teratoma ; noted left ovarian mass (Figure 1a- axial view, 1b-sagittal view) with fat density suggestive of ovarian teratoma with incidental finding of right adrenal incidentaloma (Figure 2a-axial view, 2b-sagittal view). Upon further corroborative history noted that patient did not have any paroxysmal symptoms suggestive of pheochromocytoma. In view of anticipation of surgery, urgent urine metanephrine to look for possibility of pheochromocytoma was sent. Only limited tests could be done to rule out pheochromocytoma as patient was on going treatment with IV Methylprednisolone.

She was not responding well, therefore she was started on IVIG for another 5 days. Urine metanephrine came back as low therefore it was unlikely to be pheochoromocytoma. Laparascopic left cystectomy was done on day 32 of admission and intraoperative findings revealed left ovarian teratoma measuring 2x3cm. A tracheostomy was also done in view of prolonged intubation. Post operatively, there was no significant change in her neuropsychiatric status. Final histology showed mature cystic teratoma. She was started on high dose oral Prednisolone after completion of IVIG. She

had stormy post operative recovery, complicated by sepsis secondary to pneumonia. On the day 12 of surgery, her GCS dropped to E1VTM5 , BP was persistently low measuring 80/56mmHg despite on triple inotropes and she was not able to be resuscitated.

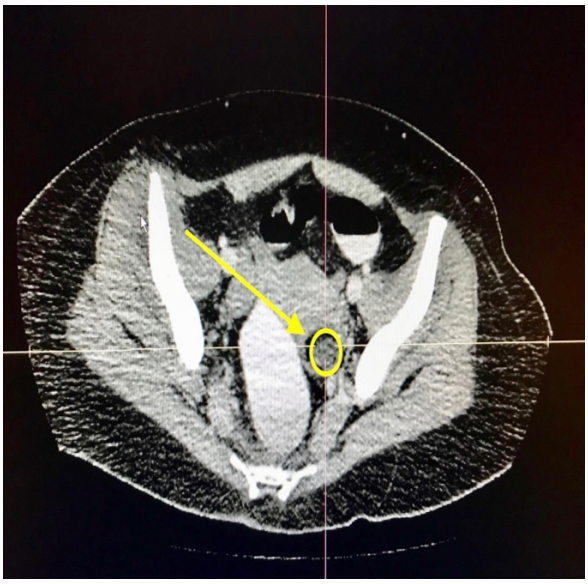

Figure 1a. Axial view of Left Ovarian Teratoma

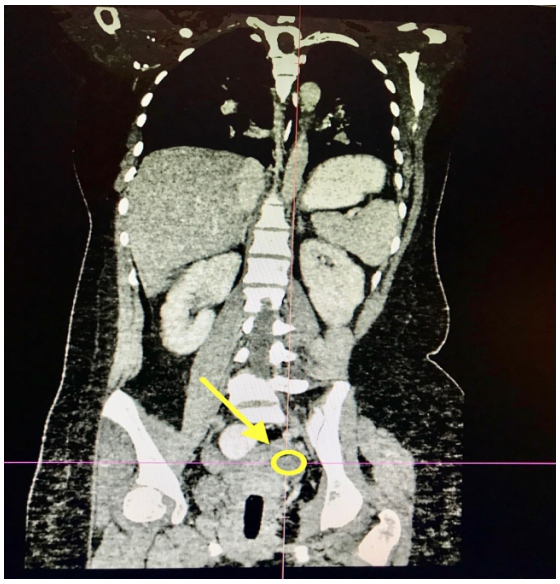

Figure 1b. Coronal view of Left Ovarian Teratoma

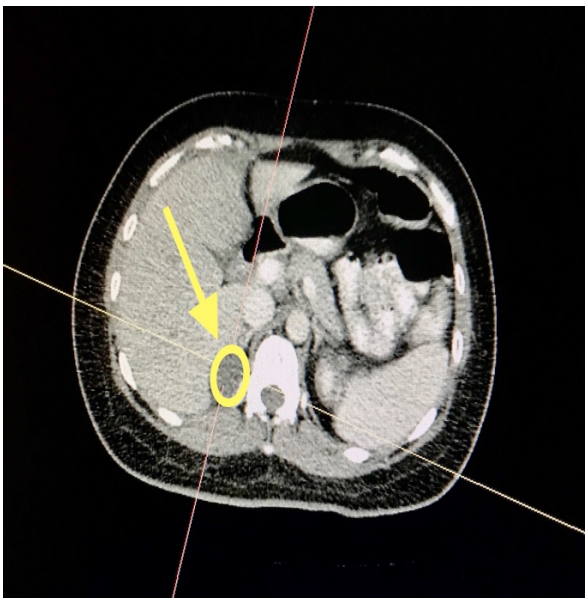

Figure 2a. Axial view of right adrenal incidentaloma

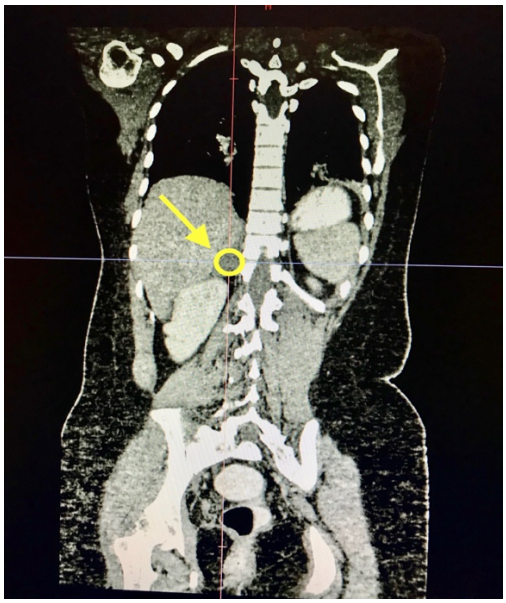

Figure 2b. Coronal view of right adrenal incidentaloma

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is the second most commonest autoimmune disorder which is often paraneoplastic in nature. Even tough the majority of patients about 80% of them are women, typically young women with teratomas, about 20% of cases are seen in men [3]. It is crucial to be aware that it is increasingly recognised in men and children as well as those in the absence of tumors . There have been cases reported in individuals from 8 months to 85 years of age, however the median age at symptom onset is estimated to be 21 years [5, 9]. The presentations may vary, therefore posing diagnostic challenge to the clinicians, especially to psychiatrists due to the prominent neuropsychiatric manifestation, about 77% of patients are initially seen by psychiatrists [9]. There are several characteristic features of this disorder. About 86% had headaches, low grade fever or viral like illness (headache, respiratory or gastrointestinal symptoms) in the weeks prior to acute presentation in case series of 100 individuals with encephalitis. Psychiatric manifestation such as agitation, bizarre and disinhibited behaviour, delusions and auditory and visual hallucinations are prominent. In our series, both patients presented with prominent psychiatric manifestation but the delusions were poorly formed and non-systematised unlike those seen in functional psychoses. Patients can also present with cognitive dysfunction such as short term memory loss and concentration difficulties [12]. In addition to epileptic seizures, patient often develop dyskinetic movements which include dyskinesias, choreathetoid movements, dystonic posturing and abnormal ocular movements which may often be mistaken for seizures. Both the patients discussed above had abnormal movements in which the male patient was misdiagnosed to have seizures complicating the dilemma in diagnosis and further delaying the specific treatment. Therefore, it is important to differentiate between complex partial seizures and movement disorders as they respond to different therapeutic interventions. Seizures often will be relatively short in duration, lasting minutes while movement disorders may have prolonged or continuous symptomatology. On top of that, seizures may occur during sleep, while movement disorders in general do not. Subsequently, decreased responsiveness and consciousness, sleep disturbance, hypoventilation, autonomic instability and catatonia may manifest as later-stage symptoms [9].

The diagnosis of encephalitis should be considered in patients with acute onset of psychiatric symptoms with neurologic findings, or symptoms unresponsive to anti-psychotic medication.

Muscle rigidity, increased muscle enzymes (ie, creatinine phosphokinase), rhabdomyolysis are symptoms specific to anti-NMDAR encephalitis without presence of anti-psychotic medication. However, the clinical picture can be obscured, calling Neuroleptic Malignant Syndrome into question after the initiation of antipsychotics for treatment of aggression, agitation and hallucinations. Haloperidol, should be cautiously used it can intensify movement disorder an can further complicate the clinical picture.

In obtaining a diagnosis, serum and CSF studies for markers of viral and autoimmune causes of encephalitis, MRI and electroencephalogram (EEG) may be useful. Brain magnetic resonance imaging scans have been reported normal in 70% of cases while hyperintensities in a variety of regions of the brain was noted in the remainder of the 30% of cases. More than 90% of patients

have EEG abnormalities [5, 13] which may show non-specific slowing or slow continuous rhythmic activity and it is particularly helpful to distinguish between a encephalitis and primary psychiatric disorder [12]. Definitive diagnosis of NMDAR encephalitis is made when anti-NMDA-receptor antibodies are detected in the blood or CSF [2, 5].
After establishment of diagnosis, first concern in female patients should be screening for an ovarian teratoma. The first line of the imaging modality to look for teratoma would often be CT scan. Transvaginal or transrectal ultrasound scan be done in cases where CT scan is negative as it may be superior than CT scans in detecting small ovarian tumors [14].

Management of this condition should be focused on the immunotherapy, detection and removal of the teratomas. Treatment with corticosteroids and intravenous immunoglobulins (IVIg) or plasma exchange should be the first line of treatment together with the tumor removal. Additional treatment with second-line immunotherapy (rituximab, cyclophosphamide or both) should be considered in patients showing little or no response to the first line of immunotherapy. Majority of patients, about 75% of patients achieve full recovery and the remaining 25% suffer from severe disability with mortality rates of 4-7%. Delay in identification and treatment of the disease is proven to be lethal with irreversible hippocampal damage [15].

Conclusion

Anti-NMDAR encephalitis should increasingly be suspected in patients presenting with rapid change of behaviour or psychosis, abnormal postures or movements, seizures and variable signs of autonomic instability. A basic understanding of the clinical findings, differential diagnosis and treatment of this illness is proven to be important as the prognosis is good with early treatment. It is extremely important to initiate immediate specific treatment which includes immunotherapy and tumor removal. Management of both, the cause and symptoms has proven to be clinically challenging and the initiation of antipsychotics is not without risk [12]. The neurologist and psychiatrist should work along side in managing this potentially lethal syndrome of psychiatric and neuromotor dysfunction in patients for a better outcome.

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