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Case Report

Rapid deterioration of a case of anti–N-methyl-D-aspartate receptor encephalitis with an ovarian teratoma, mimicking viral encephalitis

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Abstract

Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis has recently emerged as an autoimmune encephalitis syndrome. Younger females are more likely to develop this condition which usually presents as a multistage illness with predominant neuropsychiatric manifestations. It is associated with the neuroglial surface antibodies developing against NMDAR. The association of ovarian teratoma has been well recognised in this condition and tumour resection will intensify the recovery of the illness along with immunotherapy. We present a case of 19-year-old female who presented with acute onset of fever, encephalopathy and facial myorhythmia mimicking acute viral encephalitis. Her clinical status deteriorated within a short period. Later, her CSF became positive for NMDAR antibody and a right ovarian teratoma was detected. Her clinical status markedly improved with immunotherapy and excision of the teratoma following a diagnosis of Anti-NMDAR encephalitis. As a potentially treatable neurological condition, clinicians should be aware of this autoimmune encephalitis syndrome causing encephalitis.

Key words:

Anti-NMDAR encephalitis, autoimmune encephalitis syndromes, ovarian teratoma, Paraneoplastic Encephalitis

Introduction

Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis was first reported by Dr. Josep Dalmau and colleagues in 2007 (1). Anti-NMDAR encephalitis is linked with antibodies against the GluN1 component of the NMDAR (2). The pathogenicity of these auto antibodies was shown in cultured neurons and in-vivo models (3). This condition is described as a multiphase disease with a myriad of clinical features including viral prodrome like symptoms, psychiatric symptoms, encephalopathy, seizures, movement abnormalities, cognitive dysfunctions, dysautonomia and sleep abnormalities. Because of the predominant psychiatric symptoms, the patient may be misdiagnosed as schizophrenia or mania (4). The psychiatrists and physicians may not be completely aware of this condition and misdiagnosis may occur especially in resource poor settings. Anti-NMDAR encephalitis should be considered by clinicians as a differential diagnosis for acute psychiatric symptoms in young patients because it is a treatable condition with favourable outcome. Here, we describe a case of young female who had acute onset of fever, encephalopathy and orofacial dyskinetic movements mimicking viral encephalitis.

Case History

A 19-year-old female had a mild febrile illness associated with flu like symptoms for three days. She had vomiting, headache followed by behavioural changes including agitation, abnormal laughing, crying and reduced talk. She was admitted to the hospital on the 5th day of illness. She did not have any features of a connective tissue disorder, or recent history of travel and substance abuse. Her past medical history was not significant. On admission, her Glasgow coma scale (GCS) was 14/15, orofacial dyskinetic movements were noticed and her haemodynamic parameters were stable.

Initially, she was treated for viral encephalitis with acyclovir. She had a normal range of white cell with normal differential count (8.8x109/L), haemoglobin of 10.96 g/dl, platelets of 320,000/mm^3 and normal inflammatory markers (ESR 17 mm1st hr, CRP<6 mg/l). Her liver function, serum creatinine, serum electrolytes including calcium were normal. A cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis (polymorphs-nil, lymphocyte-12/mm^3) with normal protein. Blood, urine, and CSF cultures were sterile. CSF TB-PCR, HSV-PCR and JE antibody were negative. Anti-TPO antibody was negative with normal

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TSH level. Her MRI brain was normal. EEG showed diffuse slowing of waves suggestive of encephalopathy. Anti-nuclear antibody was positive in 1:80 (nuclear fine speckled pattern), but Anti DsDNA was negative. Her C3 and C4 complement levels were normal.

On the 3rd day of admission, despite the treatment with intravenous acyclovir she clinically deteriorated with low GCS and subsequently patient had to be intubated. At this point, possibility of autoimmune encephalitis was entertained, and IV methylprednisolone pulses were started. Her CSF became positive for NMDA receptor antibody. After completion of five doses of methylprednisolone pulses, oral prednisolone 60mg/day was started. From the 12th day of admission, six cycles of plasma exchanges were given for further augmentation of the management of autoimmune encephalitis. Two doses of Rituximab were also given. Azathioprine was started as a steroid sparing agent.

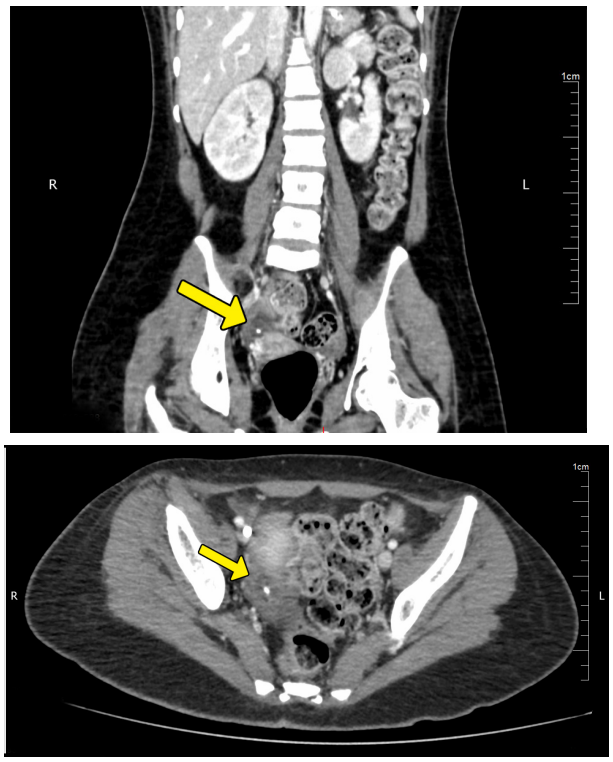

Figure 1 *computed tomography of abdomen revealed a right adnexal mass (arrow) with fluid density and a foci of calcification*

During the search for an ovarian teratoma, computed tomography of the abdomen (Figure 1) revealed a right adnexal mass measuring 23mm x 33mm. Her ß-HCG and CA-125 were negative.

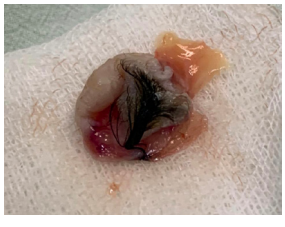

Figure 2 *Specimen of ovarian teratoma of this patient*

On the 24th day of admission, she underwent cystectomy of the right ovary (Figure 2). Histology of the specimen revealed a mature cystic teratoma comprising predominantly ectodermal and mesodermal elements. The cyst wall was lined by stratified squamous epithelium with the underlying tissue containing sebaceous glands, eccrine sweat glands, and hair follicles. There were lymphoid clusters as seen in ovarian teratoma with NMDAR encephalitis. Areas of adipose tissue, bone, glial tissue, focal choroid plexus formation, foci of Immature cartilage and immature mesenchymal tissue were also present (Figure 3).

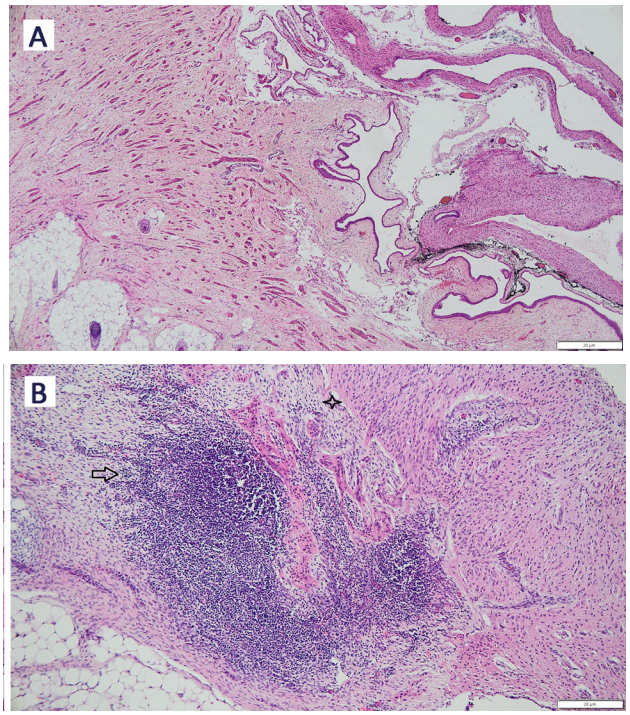

Figure 3 *Microscopic appearance of ovarian teratoma with H&E staining.* ***A:*** *Benign cystic teratoma with tissues derived from all three germ layers (x40),* ***B:*** *Benign cystic teratoma with lymphoid clusters* ***(arrow)*** *around glial tissue* ***(star)*** *(x100).*

After six weeks of ICU care, she was transferred to the neurology ward. One week later she was discharged on a tail off regime of oral prednisolone and azathioprine, almost in the premorbid condition without any residual neurological functional deficits.

Discussion

Paraneoplastic Encephalitis associated with ovarian teratoma was initially described in four young women in 2005 by Vitaliani et.al (5). After couple of years, it was recognised as Anti-NMDAR encephalitis by Dalmau and Bataller (1). A case series of 100 patients and analysis done by Dalmau J et.al showed that the median age of presentation was 23 years, and 91 cases were

women (6). Anti-NMDAR encephalitis was identified >4 times as frequently as viral cause as an aetiology of encephalitis within the cohort study of California Encephalitis Project. (7) A prospective study done by Armangue et. al showed that autoimmune encephalitis occurred in 14 patients (27%) with post herpes simplex encephalitis and 9 patients had NMDAR antibodies. (14)About 50% of female patients in between age 18 and 45 are had ovarian teratomas. (15)

Anti-NMDAR encephalitis is associated with antibodies that react with neuronal cell membrane proteins supporting an immune related pathology (7,8) These antibodies are against the GluN1 subunit of the NMDA receptor (2). Furthermore, introduction of immunoglobulins into hippocampal neuronal culture caused a marked reduction of postsynaptic NMDAR that was reversed after elimination of those immunoglobulins (6).

Table 1 Diagnostic criteria of Anti-NMDAR encephalitis

Diagnostic criterion	Our patient
Rapid onset (< 3 months) of at least four of the six following major manifestations:	
1. Altered behaviour (psychiatric) or cognitive dysfunction	Agitated behaviour, unprovoked laughing and crying
2. Speech dysfunction (pressured speech, reduced speech, mutism)	Abnormal speech including less talk
3. Seizures	Absent
4. Dyskinesias, rigidity/abnormal postures, and abnormal movements	Orofacial dyskinesia
5. Reduced conscious level	Reduce responsiveness and consciousness
6. central hypoventilation or Dysfunction of autonomic system	Hyperthermia
At least one of the following investigations	
1. Abnormal electro encephalogram (focal or diffuse disorganised or slow activity, epileptic activity, or extreme delta brush)	Slow activity in electro encephalogram
2. CSF with pleocytosis or oligoclonal bands	Lymphocytic pleocytosis
Exclusion of other reasonable conditions (infection, metabolic disorders, neoplasm)	Excluded other reasonable causes

Anti-NMDAR encephalitis initially have a prodromal phase of mild fever with nonspecific symptoms followed by a psychiatric phase, usually within two weeks, characterized by behaviour problems, agitation, delusions, hallucinations, and hyper-religiosity. Then Neurological phase will follow and is characterized by decreased responsiveness. Abnormal movements particularly orofacial dyskinesias will take place as in our case. Other abnormal movements include choreoathetoid movements, dystonia, opisthotonos, and oculogyric crisis. Autonomic instability will occur, characterized by unstable heart rate, increased salivation, hypotension, hyperthermia, and hypoventilation (9). All these phases manifested in our patient within a shorter period than usual.

Cerebrospinal fluid shows lymphocytic pleocytosis, mild elevation in proteins in most of the patients (2,6). EEG abnormalities are seen in most of the patients as a nonspecific slow activity (2,6). MRI-Brain is not significant in more than half of the patients. Definitive diagnosis is made by finding the antibodies against NMDAR in CSF or serum. A diagnostic criterion proposed by Graus F et.al with comparison with our patient was shown in table 1 (10)

A retrospective study done by Zhang et.al demonstrated that autoantibodies were frequently found in anti-NMDAR encephalitis patients than in healthy controls (13). Our patient also had ANA positive titre 1:80. Furthermore, that study found a negative correlation between prognosis of anti-NMDAR encephalitis and autoantibodies.

Immunotherapy typically corticosteroids, intravenous immunoglobulins or plasma exchange are the first line treatment in addition to the excision of any tumours especially ovarian teratoma. Second-line immunotherapies are rituximab or cyclophosphamide which are rarely necessary. Outcome of treatment will be more favourable in patients who underwent a tumour excision. There are cases of ovarian teratomas reported years after onset of disease, especially in those who had a slow recovery (11). Anderson et.al described a refractory case in whom the excision of an ovarian teratoma, not visible on pelvic imaging, resulted in marked clinical outcome (12).

Conclusion

We present a case of NMDAR autoimmune encephalitis which presented with acute fever, encephalopathy and psychiatric manifestations mimicking an acute

viral encephalitis. Clinicians need to be very vigilant about this condition in a setting of acute encephalitis, irrespective of virological confirmation like HSV. Prompt initiation of immunotherapy and tumour resection has been shown good results with a speedy recovery.

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