

Meningitis as early manifestation of anti-NMDAR encephalitis

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Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently discovered immune mediated encephalitis. The syndrome typically occurs in children and young adult with initial presentations of psychiatric symptoms, seizures, followed by abnormal movement and dysautonomia. There is association with ovarian teratoma. We report here a 16-year-old girl with anti-NMDAR encephalitis, who present with meningitis as initial symptom, confirmed by pleocytosis in the cerebrospinal fluid and leptomeningeal enhancement in MRI. She subsequently manifested the more typical manifestations of oro-facial dyskinesia and choreoathetosis. The diagnosis was confirmed by the presence of anti-NMDAR antibody. She was treated with immunotherapy with clinical improvement and drop in the level of autoantibody. However the patient died due to septicemia.

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune mediated disease that was first reported in 2005. Since then, the disease has been increasingly recognized. Initial presentations are usually abnormal psychiatric problem, seizure, or impairment of consciousness followed by abnormal movement such as orofacial dyskinesia, autonomic dysfunction and hypoventilation. There is associated autoantibody against NMDAR receptor (NR1 subunit) which is thought to be pathogenic. Ovarian teratoma has also been known to be associated with this condition. Early diagnosis and treatment with immune therapy or removal of tumor could improve the outcome.¹ Here we report a patient with atypical presentation of meningitis, who subsequently manifested the more typical manifestations of anti-NMDAR encephalitis.

CASE REPORT

A 16-year-old girl presented with headache and low-grade fever for one week. The headache was described as persistent dullness at the occipital area accompanied with nausea and vomiting. Physical examination revealed mild elevated body temperature (38 degree Celsius), with no other systemic abnormality. Neurological examination showed fully consciousness and

normal cognition. There was bilateral sixth nerve palsies. Motor power was normal with increased tones in all extremity and Babinski's sign both sides. There was also stiffness of neck. Investigations with complete blood count showed leukocytosis with predominant polymorphs. MRI brain showed leptomeningeal enhancement along sulci at bilateral parieto occipital and cerebellum regions shown by Figure 1b. T2 FLAIR showed high signal lesion at left cerebellum (Figure 1a). Cerebrospinal fluid (CSF) revealed high opening pressure (>60 cmH₂O), pleocytosis (total white blood cells were 273 cells/ul, lymphocyte predominant), elevated protein (220 mg/dl) and normal glucose. Cryptococcal antigen, polymerase chain reaction for tuberculosis, herpes simplex virus type I, II; Japanese encephalitis and dengue virus serology studies were all negative. She was provisionally diagnosed to have tuberculous meningitis, and was given anti-tuberculous drugs, steroid and repeated lumbar puncture to reduce the intracranial hypertension. However, her conscious level continued to deteriorate. EEG monitoring showed diffuse slow delta activities without epileptiform discharge. She developed oro-facial dyskinesia, choreoathetosis and hypersalivation after one week.

Diagnosis of anti-NMDAR encephalitis was suspected, and the diagnosis confirmed by demonstration of anti-NMDAR antibody by both

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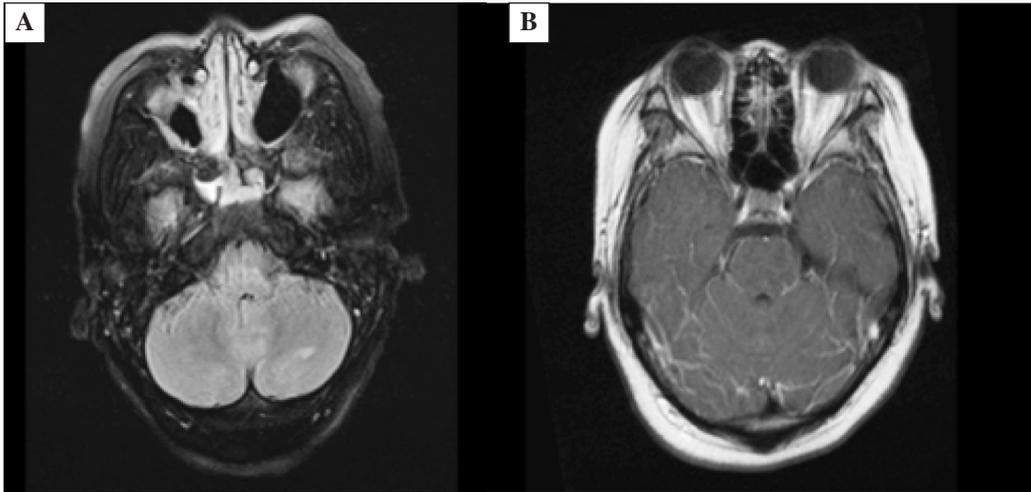


Figure 1. MRI FLAIR image shows high signal intensity at Left cerebellum (A). T1 with gadolinium shows prominent leptomeningeal enhancement in the sulci around cerebellum compatible with meningitis (B)

immunohistochemistry assay and cell-based assay (Euroimmun®) (Figure 2). As for the antibody tests, for tissue immunohistochemistry assay, the mouse brain composite substrate (hippocampus, forebrain and cerebellum) was used. Anti-NMDA receptor antibody was detected by fluorescence-conjugated goat antibody to human IgG. The result is considered positive when the staining patterns are defined at hippocampus and granular layer of cerebellum. For cell-based assay, the HEK293 transfected with NR1 subunit of NMDA receptor is used as substrate. The staining pattern on cell surfaced is considered positive. Both methods are all compared with positive control.

Ovarian teratoma was found at left ovary (size 3.2×2.7 cm) and an unexpected fetus of about seven weeks size estimated by trans abdominal

ultrasound examination. After discussion with her family, the pregnancy was terminated. She was subsequently given immunosuppressive treatment, with intravenous methylprednisolone 1 gram for five days, followed by plasma apheresis for five cycles. Oophorectomy was also performed in which the pathology examination confirmed the diagnosis of mature cystic teratoma. Oral prednisolone was given as maintenance therapy. Two week later, the orofacial dyskinesia and conscious level improved. A followed up serum anti-NMDAR antibody study became negative after an interval of eight weeks. Unfortunately, the patient later died from severe septicemia and cardiovascular collapse.

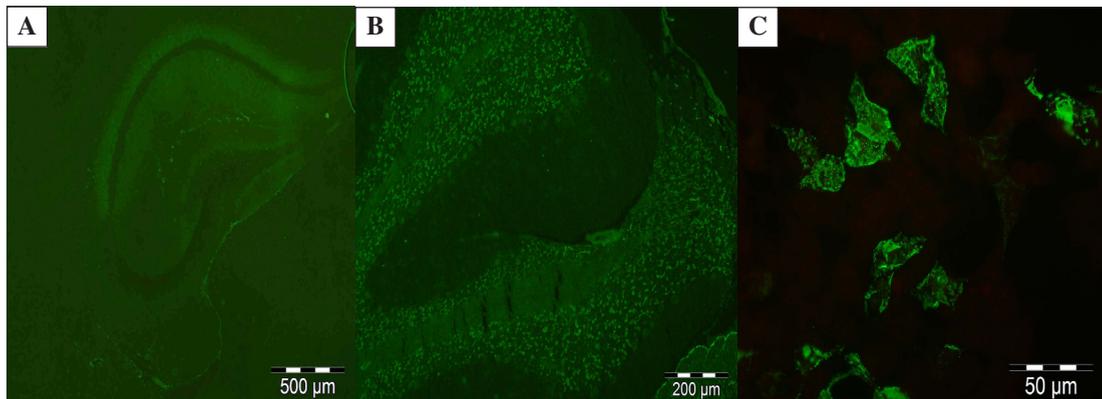


Figure 2. The mouse brain composite substrate demonstrated the fluorescence staining pattern at hippocampus (A) and granular layer of cerebellum (B). HEK293 cells transfected with NR1 subunit demonstrate fluorescence staining pattern on the cell surface (C).

DISCUSSION

There are differences in the initial presentation of anti-NMDAR encephalitis in the different age group. Seizure and abnormal movement are common in young patients (< 12 years old), whereas behavioral change and seizure are often seen in adult.¹ It has been said that 38% of patients had underlying neoplasms. Tumor is more commonly seen in female of 12-45 years old as compared to the younger patients. The common tumors reported are ovarian teratoma (98%), extra ovarian teratoma (2%), and rarely lung, breast, and testicular tumors.¹

Atypical presentations of cerebellar ataxia, hemiparesis, extensive myelitis have been reported in anti-NMDAR encephalitis.^{2,3} The encephalitis has also been reported to occur after herpes simplex encephalitis.⁴ Our patient had unusual presentation of meningitis, manifesting with the initial symptoms of headache and stiffness of neck without impairment of consciousness. CSF analysis confirmed the meningeal inflammatory process of pleocytosis, elevated protein and high opening pressure. This was also confirmed by the prominent diffuse leptomeningeal enhancement in the MRI. This was followed by other features of encephalitis manifesting later. Dalmau *et al.*⁵ in the review of the clinical experience of anti-NMDAR encephalitis, mentioned from personal observation that “transient increase of intracranial pressure has been recorded in a few patients.” Lim *et al.*² recently reported an 18 years old male with anti-NMDAR encephalitis, who presented with seizure and CSF pleocytosis one week after new onset headache without fever, and diagnosed as viral meningitis. The patient was readmitted later with choreoathetotic movement and impaired consciousness. The repeat lumbar puncture showed a high CSF opening pressure of 55 mmH₂O, pleocytosis and unremarkable MRI brain. Our patient, and that of Lim *et al.*² confirmed that anti-NMDAR encephalitis can present with meningitis.

MRI imaging are unremarkable in 50% of patients of anti-NMDAR encephalitis. The findings reported are hyperintense signal in T2 or FLAIR images in hippocampus, cerebellum, cerebral cortex (especially frontal lobe), insular region, basal ganglion, brain stem and spinal cord.⁵ Our patient had hyperintense signal in FLAIR at cerebellum with prominent leptomeningeal enhancement at bilateral parieto-occipital and cerebellar regions.

EEG finding of our patient was that of non-

specific delta activities predominately at frontal region without epileptiform discharge. We did not see the unique electrographic pattern of “extreme delta brush”, said to be found in 33% of anti-NMDAR encephalitis patients, associated with prolong hospitalization.⁵

Anti-NMDAR encephalitis during pregnancy has also been reported, and some of the patients have carried the pregnancy to term and delivery healthy babies.⁷ The effect of pregnancy on the encephalitis has not been studied. It is not certain whether pregnancy aggravates the encephalitis, or contributes to the unusual initial presentation of meningitis in our patient.

To date high dose steroid, plasma exchange or IVIG and tumor removal has been the common first line treatment of anti-NMDAR encephalitis. Our patient has some clinical response with change in the anti-NMDAR antibody status after steroid, plasma exchange and removal of the ovarian tumor.⁶ Unfortunately she died from medical complications.

In conclusion, meningitis can be a presenting feature of anti-NMDAR encephalitis.

DISCLOSURE

Conflict of interest: None

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