Case Report

Anti-NMDA Receptor Encephalitis: Four Case Reports and Literature Review

Kongkiat Kulkantrakorn, MD[1,2] ; Chattrabongkot Chokaouychai[1] ; Praween Lolekha, MD[1]

Kongkiat Kulkantrakorn, MD

Abstract

Anti-NMDA receptor encephalitis is increasingly being recognized as one of the causes of non-infectious encephalitis. Here, we report four female patients with this disease who had a different clinical course and outcome. The patients are all female aged below 45 years old, especially teenagers, and it is usually accompanied by ovarian teratoma. The disease often starts with a prodromal phase of flu-like symptoms, followed by progression into major typical symptoms: prominent psychiatric disorder or bizarre behavior, seizure, abnormal movement, dysfunctional speech, memory deficit, alteration of consciousness and autonomic instability. Recognizing this syndrome and confirming with antibody testing will more likely lead to a favorable outcome. Prompt immunotherapy should be initiated, common protocols are high doses of steroids, plasmapheresis and intravenous immunoglobulin. However, the treatment protocol and long-term management is still not established.

Keywords: Anti-NMDA receptor encephalitis, immunotherapy

[1] Faculty of Medicine, Thammasat University, Pathumthani, Thailand
[2] Neuroscience Center, Bangkok Hospital Bangkok, Thailand

** Address Correspondence to author:*
Kongkiat Kulkantrakorn, M.D.
Neurology Division, Department of Internal Medicine
Faculty of Medicine, Thammasat University
Pathumthani 12120, Thailand
email: kongkiat1@gmail.com

Received: June 22, 2018
Revision received: June 22, 2018
Accepted after revision: July 2, 2018
BKK Med J 2018;14(2): 66-71.
DOI: 10.31524/bkkmedj.2018.09.012
www.bangkokmedjournal.com

Acute encephalitis is a severe neurological disorder which leads to rapid progressive encephalopathy. Central nervous system (CNS) infections are generally known to be the main causes of the disease, however it has also been increasingly recognized that another important cause which should not be neglected is autoimmunity. Autoimmune encephalitis often manifests as behavioral disturbances, abnormal movement, seizures and cognitive impairment. It is associated with the antibodies against neuronal surface protein, ion channels or receptors.[1] The common ones are antibodies to N-methyl-D-aspartate (NMDA) receptor, leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2) and gamma-aminobutyric acid (GABA). Each antibody has different patient characteristic and clinical profiles.

Anti-NMDA receptor encephalitis is the most common among these and is a well-known antibody-associated encephalitis, frequently present in adolescent females younger than 45 years old.[1-3] The inflammatory process is driven by cerebrospinal fluid (CSF) IgG antibodies against GluN1 subunit of NMDA receptor (a synaptic receptor).[1] This is due to the fact that anti-NMDA receptor encephalitis has typical clinical signs and clinical manifestation. A specific investigation is helpful for diagnosis to facilitate decision-making on treatments of choice from the early stages of the disease. The earlier the detection is made, the more effective the treatment becomes.[1-5] The illustrated cases presented in this report contain clear manifestations and this is considered helpful towards improving the clinical practice for the diagnosis of autoimmune encephalitis.

Case Report #1

A 19-year-old Thai female, with no known underlying medical condition, presented with aggressive and self-injuring behaviors. The patient described that, two weeks before the incidence, she suffered from academic and personal relationship-related stress. It caused her to stay in her room and avoid socialization.

Ten days prior to being admitted into the local hospital, she had a generalized tonic spasm in her limbs while in her classroom, with eyes bulging and rolling upwards. The symptoms lasted for less than a minute during which she could still respond to people calling her name. There was no urinary and fecal incontinence. The attack repeated thrice without clear precipitating factors. She was sent to a local hospital but was later discharged since no abnormality was found.

Seven days later, she developed repeated seizures with the same characteristics, but with an increase in duration to approximately 2-3 minutes. The symptoms faded and stopped without any use of medication. After the onset, she would sleep for 5-10 minutes. Symptoms regularly repeated every 2 hours for 4 times. There was no fever, weakness of extremities, or headache. Then, she was admitted to a local hospital; her computed tomography (CT) brain scan and lumbar puncture were unremarkable. During this period, she did not experience any seizures; therefore there was no further administration of anti-epileptic drugs. She was, at that time, able to take care of herself and was well-oriented to time, place and people. However, a few days later, she started talking to herself, shouted, got out of bed and refused to sleep. At this point, her family deemed that there was no improvement in her condition and decided to request for her to be discharged. On the way back home, she was agitated and attempted to jump out of the car although she denied visual and auditory hallucination.

Two days prior to this hospital admission, the symptoms worsened. She talked to herself in repeated sentences for a long time and refused to receive any advice. She was obviously confused and aggressive – repeated ranting and shouting, walking around the house naked, wandering around the house at night. One day prior to being admitted, the patient took a knife and ran into the toilet attempting to commit suicide. Her family thus decided to bring her to the hospital.

The family described the patient's usual condition as a timid and polite person with good academic performance. She had no prior chronic diseases or psychiatric illness, denied the use of any illicit drugs. However, at the age of 10, she was admitted to a hospital with the symptoms of generalized tonic-clonic spasm and changes of behavior. After one-month period of admission, she was prescribed with an antiepileptic for 1 year. The patient did not take any more drugs after the seizures ceased.

Physical examination revealed confusion, disorientation, agitation with dystonia and orofacial dyskinesia. Complete blood count and routine blood chemistry were normal. CSF studies showed a normal profile with no microorganism found in gram stain and culture. Polymerase chain reaction (PCR) for Herpes and serum Cryptococcus antigen testing were negative. Anti-HIV titer and Treponemal testing (VDRL/ TPHA) were also non-reactive. Chest x-ray showed no evidence of fungal or mycobacterial infection. Electroencephalogram (EEG) found no evidence of epileptic activity, but extreme-delta brush pattern was noted (Figure 1). MRI brain (epilepsy protocol) with gadolinium enhancement showed only a small T2W/FLAIR-hyperintensity lesion with no restricted diffusion on DWI and no enhancement on post contrast study at a deep white matter of the left frontal lobe. Toxic screening was negative. NMDA receptor antibody was present in both her serum and CSF. Chest and whole abdominal CT scan showed no significant mass.

She was treated with plasmapheresis and pulse methylprednisolone 1gm intravenous (IV) once daily for 5 days, then switched to high dose oral prednisolone. After 1 month-admission and supportive treatment, she was discharged from hospital, with a prescription of oral prednisolone. Azathioprine was added to reduce steroid side effects. At 6 months, her cognitive function and activities of daily living became normal. However, after taping down her antiepileptic drugs and steroid, her seizure relapsed and it progressed to refractory status epilepticus. The seizures were difficult to control with more than four antiepileptic drugs. After restituting high dose steroid and plasmapheresis, her seizures gradually resolved. She was hospitalized for over one month with gradual recovery to her baseline condition in one month. Repeat gynecologic examination and transvaginal ultrasound revealed no evidence of ovarian tumor. She was still on two antiepileptic drugs, prednisolone and cyclosporine.

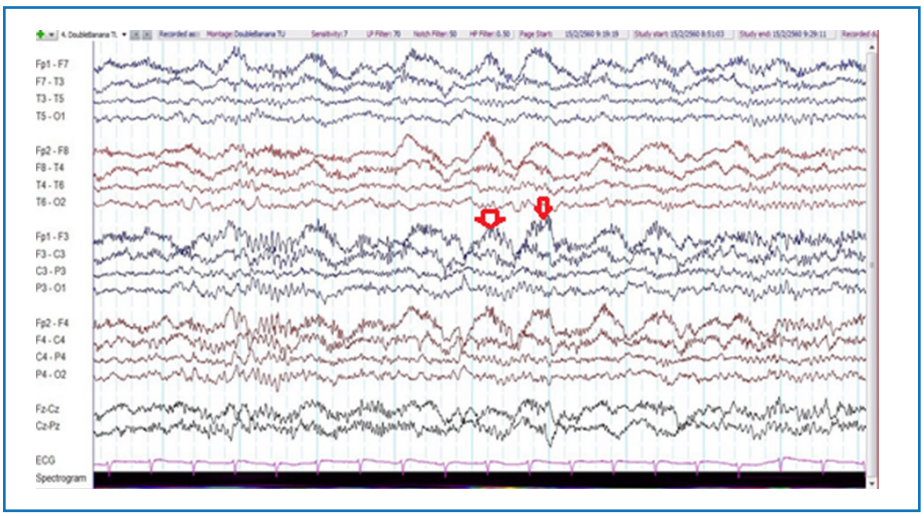

Figure 1: Electroencephalogram (EEG) of case 1 revealed generalized extreme delta brush without epileptic activity (arrow).

ISSN 2287-0237 (online)/ 2287-9674 (print)

Case Report #2

The patient is a 27-year-old female who presented with acute psychosis and behavioral changes for 4 weeks. She gradually developed incoherent speech, visual and auditory hallucination, inappropriate behavior and confusion in 2 weeks and became less responsive to commands. At times, she had abnormal neck movement and myoclonic jerk at both arms. One day prior to admission, generalized tonic-clonic seizure developed. After recovering from a seizure, her consciousness fluctuated and she did not respond to verbal commands and had minimal speech output. Her underlying disease included Hashimoto thyroiditis which had been under control.

Initially, she was treated with many antipsychotics, antidepressants, sedatives and antiepileptic drugs with partial response in her psychotic symptoms and memory. A routine investigation was unremarkable. During admission, generalized tonic-clonic seizure developed and autoimmune encephalitis was suspected. Therefore, further investigation was performed. CSF paraneoplastic antibody was positive for anti-NMDA receptor antibody, while the antibody in the serum was negative. Thyroid function test and thyroglobulin/TPO antibody were within normal limits. Extensive laboratory investigations for other autoimmune diseases were unremarkable. Computed tomography of the whole abdomen was negative for intra-abdominal malignancy and teratoma. Small ovarian cysts were present on both sides and they were thought to be benign or physiologic in nature.

After the diagnosis was made, she was treated with one course of plasma exchange followed by a high dose of intravenous pulse methylprednisolone. Her psychotic symptoms and seizure had resolved in one month. After 2 months of hospitalization, she was discharged home with some assistance in basic activities of daily living. Regarding the specific treatment, prednisolone (1 mg/kg/day) and azathioprine (2 mg/kg/day) were prescribed. Her condition, especially memory and activities of daily living became normal after 3 months. Then, she was able to return to work full time afterwards. The immunosuppressant and valproic acid were slowly tapered without recurrent symptoms.

One year later, surveillance pelvic ultrasound showed a large cystic lesion (3.8 x 5.3 cm) at her right ovary. Then, she was operated on and found to have a bi-lobulated ovarian cyst. Pathology showed a mature cystic teratoma, consisting of hair, sebum and bony tissue (Figure 2). Since then, all the medication has been tapered off over 6 months. She remained asymptomatic with complete recovery for the past 2 years of follow up.

Case Report # 3

A 20-year-old female college student presented with a severe headache and confusion for 2 weeks. Two weeks prior to admission, she had episodic, but progressive bifrontotemporal headache which lasted several hours to days. Ten days later, she became confused and had inappropriate speech. Initial evaluation at a local hospital was unremarkable and symptomatic treatment was prescribed. One day later, she had a fever, more confusion and agitation. While waiting at an outpatient clinic, she had an episode of generalized tonic-clonic seizure. Then she was admitted and was found to be drowsy and did not respond to questions or commands. No focal neurological finding was noted. CT brain with contrast showed no parenchymal lesion. CSF examination revealed 8 white blood cells per millileter, with normal protein and glucose levels. Herpes viral panel in CSF was normal. Serum and CSF NMDA receptor antibody were positive.

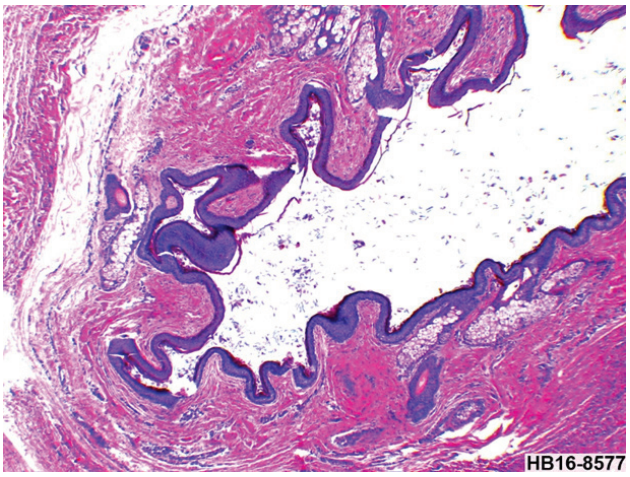

Figure 2: Ovarian cyst; Histological sections of ovarian cyst are composed of three layers of tissue component including skin with appendages, brain, adipose tissue and respiratory typed mucosa with cartilage. Patchy lymphoid aggregates are also seen.

After stabilization and IV phenytoin for seizure control, she was initially treated with IV acyclovir while waiting for the laboratory results and it was off after 3 days. After the diagnosis of NMDA receptor antibody encephalitis was made, intravenous pulse methylprednisolone was given at 1 gram per day for 5 days and followed by intravenous immunoglobulin (0.4 g/kg/day for 5 days). Oral prednisolone and azathioprine were prescribed for long-term treatment. After two months follow up, her cognitive function and headache had improved, but she was still unable to return to her study.

Case Report # 4

A 32-year-old woman with no underlying illness presented with confusion and behavioral changes for 2 weeks. She also noted abnormal oro-facial movements which usually occur at night. The initial evaluations including general blood tests, CT brain scan, and CSF analysis were unremarkable. One day before admission, she developed generalized tonic-clonic seizures and was admitted to the hospital. Her seizures were difficult to control and had progressed to refractory status epilepticus. She was transferred to the intensive care unit (ICU) for multiple antiepileptic drugs and anesthetic agents including IV midazolam, and propofol. She was initially treated with IV acyclovir, but her clinical had progressed, and

ISSN 2287-0237 (online)/ 2287-9674 (print)

oro-lingual-facial dyskinesia had been obviously observed. Even the initial CSF paraneoplastic antibody was negative for NMDA receptor antibody, limbic encephalitis was suspected. EEG also showed delta brush pattern. Then, she was treated with plasmapheresis and pulse methylprednisolone 1gm IV once daily for 5 days, and switched to high dose oral prednisolone. Repeated CSF paraneoplastic antibody at 3 months was positive for anti-NMDA receptor antibody, while the antibody in the serum was still negative. Gynecologic examination and transvaginal ultrasound revealed no evidence of ovarian tumor.

After restituting high dose steroid and plasmapheresis, her seizure gradually resolved. She was hospitalized for over three months with gradual recovery to her baseline condition in ten months. She remained asymptomatic with complete recovery for the past 3 years of follow up. She was still on two antiepileptic drugs.

Discussion

An autoimmune disorder is the common cause of encephalitic syndrome after infection, often viral and post-infectious acute disseminated encephalomyelitis. A survey from Thailand in 103 patients with encephalitis syndrome revealed no clear etiologies in 52% of cases. Nevertheless, 25 patients were found to have immune-mediated encephalitis.[6] Five patients had the NMDA receptor antibody and two of them had ovarian tumors. Therefore, autoantibody-associated encephalitis should be placed in the differential diagnosis of encephalitis syndrome.[6]

Anti-NMDA encephalitis predominantly affects young adults (under 45 years old) with female sex predominance (4:1).[1-4] It has typical and predictable clinical manifestations with a two-week prodromal phase of flu-like symptoms, followed by multi-stage progression. Eight categories of major symptoms include prominent abnormal psychiatric disorder or developing bizarre behavior, seizure, abnormal movement, dysfunctional speech, memory deficit, alteration of consciousness, and autonomic instability (e.g. bradycardia, tachycardia hyperthermia, fluctuation of blood pressure and central hypoventilation requiring mechanical ventilator).[2-3] These patients generally show decreased responsiveness, varying from agitation to catatonia. The symptoms are usually followed by abnormal movement or posture, including oro-lingual-facial dyskinesia, limb and trunk choreoathetosis, oculogyric crisis, dystonia, rigidity, and opisthotonic postures.[4]

Diagnosis of the disease could be confused and delayed due to the fact that its typical clinical manifestations are also present in other neurological and psychiatric disorders. Non-systematized fragmented psychosis with absent or mild delusion (as opposed to other functional psychosis) is of a high index of suspicion. It is reported that 77 percent of anti-NMDA receptor encephalitis patients were initially diagnosed with a primary psychiatric disorder.[5] Some abnormal movement (e.g. dyskinesia) might be initially misunderstood with seizure-like symptoms and is underestimated.[4-5] This problem even applies to oro-lingual-facial dyskinesias which are the most characteristic movements of anti-NMDA receptor encephalitis.[3] Consequently, clinical diagnosis of anti-NMDA receptor e ncephalitis should be carefully reviewed and considered in any encephalitis case, especially cases with prominent acute psychosis with abnormal behavior. The diagnostic criteria is shown in Table 1 and the information for our four cases is summarized in Table 2.

Table 1: Diagnostic criteria for anti-NMDA receptor encephalitis.[2]

Probable anti-NMDA receptor encephalitis
Diagnosis can be made when all three of the following criteria have been met:
1. Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
- Abnormal (psychiatric) behavior or cognitive dysfunction
- Speech dysfunction (pressured speech, verbal reduction, mutism)
- Seizures
- Movement disorder, dyskinesias, or rigidity/abnormal postures
- Decreased level of consciousness
- Autonomic dysfunction or central hypoventilation
2. At least one of the following laboratory study results:
- Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
- CSF with pleocytosis or oligoclonal bands
3. Reasonable exclusion of other disorders (appendix)
- Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma
Definite anti-NMDA receptor encephalitis
Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies, after reasonable exclusion of other disorders

Table 2: Summary of four cases

Case 1	Case 1	Case 2	Case 3	Case 4
Age (years)	19	27	20	32
Gender (M/F)	F	F	F	F
Clinical manifestation				
Seizure	Yes	Yes	Yes	Yes
Abnormal behavior	Yes	Yes	Yes	Yes
Autonomic instability	Yes	No	No	No
Movement disorder	Yes	Yes	No	Yes
Reduced level of consciousness	Yes	Yes	Yes	Yes
Investigation				
EEG	Delta brush pattern	Unremarkable	Unremarkable	Delta brush pattern
CSF study	Normal	Normal	8 WBC, otherwise normal	Normal
MRI brain	Small hyperintensity lesion at while matter	Normal	Normal	Normal
Tumor	No	Ovarian teratoma	No	No
Treatment				
High dose IV steroid	Yes	Yes	Yes	Yes
IVIg	No	No	Yes	No
Plasmapheresis	Yes	Yes	No	Yes
Longterm treatment	Prednisolone and cyclosporin	Prednisolone and Azathioprine	Prednisolone and Azathioprine	Prednisolone
Outcome	Complete recovery	Complete recovery	Complete recovery	Complete recovery
Complication	Epilepsy	No	Mildly impaired cognition	Epilepsy

The patient in Case 1 is a definite match to anti-NMDA receptor encephalitis. Even if the results from the CSF test in this case showed a normal profile, autoimmune encephalitis could not be ruled out. In addition, interesting results were revealed through the generalized extreme delta brush observed in the EEG (Figure 1).[7] Approximately 30 percent of anti-NMDA receptor encephalitis patients have EEG of a similar character. It is believed that the extreme delta brush is associated with anti-NMDA receptor encephalitis and prolonged illness, although specificity still remains unclear.[2] Another possible pattern found in EEG in these patients is non-specific, slow, and disorganised activity – sometimes with electrographic seizures.[4] Poorly sustained posterior dominant rhythm (PDR) was significantly associated with autoimmune encephalitis and even more predictive in anti-N-methyl-d-aspartate (NMDA) encephalitis. Simple EEG assessments can be used to help exclude AE.[8]

On the other hand, most of the patients with anti-NMDA receptor encephalitis often have a normal MRI. It was estimated that 30 percent of the patients with an abnormal MRI were mainly showing increased fluid-attenuated inversion recovery (T2-FLAIR) hyperintensity signal involving the cortical, subcortical or cerebellar region.1 This was also present in Case 1, but did not have much influence on the diagnosis.

Regarding the antibody testing, it is recommended to test in both CSF and serum. Serum testing may have false negative results in up to 14% of cases. The sensitivity of NMDA receptor antibody testing is higher in CSF than in serum. Antibody titers in CSF and serum were higher in patients with poor outcome or teratoma than in patients with a good outcome or no tumor. The titer change in CSF was more closely related with relapses than that found in serum. These findings emphasise the importance of including CSF in antibody studies, and that antibody titers can complement clinical assessment.[9] Nowadays, the assay for this antibody or autoimmune encephalitis antibody panel is widely available. Physicians should screen for this treatable disease in any patient with suspected non-infectious encephalitis or who presented with a rapid-onset psychiatric syndrome, cognitive impairment, abnormal movement, and seizure.

Furthermore, anti-NMDA receptor encephalitis is usually accompanied by the presence of an underlying tumor which is varied depending on age and sex. It was reported that ovarian teratoma was present in 58% of the female patients aged above 18 years old.[2-3] Other types of the tumor including lung cancer, thyroid cancer, breast cancer, colorectal cancer, and neuroblastoma are not common.[3-4] Only 5 percent of the male patients have an associated tumor, usually a testicular germ-cell tumor. It is interesting that treatments tend to be

ISSN 2287-0237 (online)/ 2287-9674 (print)

more effective in patients who have undergone tumor resection.[3-4] This is in agreement with some studies which have proposed that the microscopic germ cell tumor, not detectable through imaging techniques, might be the cause of prolonged illness and more incidence of relapse when compared to a detectable tumor.

Fortunately, anti-NMDA receptor encephalitis is reversible with removal of the tumor (if present) and immunotherapy. Nevertheless, obtaining the results from an antibody test still can take several weeks, and the test might not be readily accessible in various situations. If left untreated, the disease has the potential to progress into permanent neurological destruction, including autonomic instability, catatonia, status epilepticus, or coma.[1-4] Therefore, while the antibody test is being processed, patients with rapid progressive encephalopathy who meet the criteria listed in Table 1 should be regarded as possible cases of anti-NMDA receptor encephalitis and should receive immunotherapy with tumor screening. Thoraco-abdominal-pelvic imaging examinations such as ultrasound, MRI, computed tomography, and positron emission tomography may be used to evaluate any underlying neoplasm.[10] In Case 2, the initial investigation by CT scan of the whole abdomen was unremarkable. However, the repeat tumor surveillance 1 year later revealed large ovarian cyst and later found to be teratoma.

The data from a clinical trial for treatment in this disease is limited. Most treatments are based on case series or expert opinion from other autoimmune diseases. The conventional first line immunotherapy is pulse methylprednisolone, plasmapheresis or intravenous immunoglobulin. If there is no response, combination therapy may be helpful. An alternative second-line method includes rituximab or cyclophosphamide.

If the patient responds to the treatment, steroids should then be tapered off and tumor surveillance should be performed annually. Most patients with anti-NMDA encephalitis respond to immunotherapy. Second-line immunotherapy is usually effective when first-line treatments fail. Fifty-three percent of patients responded with first-line treatment. Of those who did not respond, 57% had a better outcome with second-line immunotherapy. At 24 months' follow-up, 81% had a good outcome. Outcomes continued to improve for up to 18 months after symptom onset. Predictors of a good outcome were early treatment and no admission to an intensive care unit. Twelve percent had relapsed within 2 years. Relapse of the disease often occurs when immunotherapy is reduced or discontinued.[11] Nevertheless, the treatment duration of steroid and/or second line immunotherapy is still not settled. However, tumor surveillance should be performed annually. The potential contributing factors to different outcomes of each individual case are: the severity of initial presentation; time from onset to diagnosis; underlying teratoma; intensity of immunotherapy and its related complications such as status epilepticus and systemic complications.

Conclusion

Anti-NMDA receptor encephalitis is a rapid progressive encephalopathic syndrome resulting in neuropsychiatric disorders, movement disorders and autonomic disturbances which may lead to significant morbidity and mortality. The high index of suspicion is critical in any patient with suspected encephalitis. Specific or autoimmune encephalitis antibody panel should be performed. Tumor surveillance is crucial once the diagnosis is made. Prompt treatment with immunotherapy and supportive treatment will lead to a favorable outcome and prognosis.

References

1. Dalmau J, Gruas F. Antibody-mediated encephalitis. *N Eng J Med* 2017;378:840-51.
2. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391-404.
3. Dalmau PJ, Lancaster E, Martinez-Hernandez E , et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63-74.
4. Barry H, Byrne S, Barrett E, et al. Anti-N-methyl-D-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. *Br J Psych Bull* 2015;39:19-23.
5. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; 7:1091-8.
6. Saraya A, Mahavihakanont A, Shuangshoti S, et al. Autoimmune causes of encephalitis syndrome in Thailand: prospective study of 103 patients. *BMC Neurol* 2013;13:150.
7. Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;79:1094-100.
8. Limotai C, Denlertchaikul C, Saraya AW, et al. Predictive values and specificity of electroencephalographic findings in autoimmune encephalitis diagnosis. *Epilepsy Behav* 2018;84: 29-36.
9. Gresa-Arribas N, Titulaer MJ, Torrents A, et al: Antibody titers at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol*. 2014;13: 167-77.
10. Kelly BP, Patel SC, Marin HL, et al: Autoimmune encephalitis: pathophysiology and imaging review of an overlooked diagnosis. *AJNR Am J Neuroradiol* 2017;38: 1070-8.
11. Titulaer MJ, McCracken L, Gabilondo I, et al: Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12 :157-65.