Original Article

Anti-NMDA-Receptor Encephalitis of Thai Patients: Description of a Consecutive Series of Patients over 10 Years and a Literature Review

Sapol Thepwiwatjit[1], Jiraporn Jitprapaikulsan MD[2]

[1] Medical Student; Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2] Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Anti-N-methyl-D-aspartate receptor [anti-NMDAR] encephalitis is an autoimmune encephalitis commonly associated with ovarian teratoma [OT]. Currently, there is no literature for anti-NMDAR encephalitis in Thai patients who may have different clinical manifestations compared to patients from other regions.

Objective: To evaluate the clinical characteristics, assessments, and outcomes of a series of anti-NMDAR encephalitis in Thai patients and review of the literature.

Materials and Methods: All adult Thai patients with anti-NMDAR encephalitis confirmed positive by one anti-NMDAR antibody test, either in serum or cerebrospinal fluid [CSF], and hospitalized in the Department of Medicine, Siriraj Hospital, Thailand, between 2007 and 2016, were identified from the hospital's database.

Results: Nine patients with a median age of 21 years (range 15 to 49), including eight (89%) that were female, were included in this study. Initial presentations included seizures (4 patients, 44%), psychiatric symptoms (4, 44%), and cognitive impairment (1, 11%). Chronic relapsing inflammatory optic neuropathy proceeded to encephalopathy in one patient (11%). Six patients (67%) had abnormalities in brain imaging, revealed by computed tomography with contrast or magnetic resonance imaging, or both. Leptomeningeal enhancement was present in two patients (22%). An OT was found in three out of six patients (50%), all of whom underwent tumor removal. Immunotherapy was given to all patients. Clinical outcomes were marked recovery in four patients (44%), persistent cognitive deficit and partial dependency in two (22%), and death by hospital-acquired pneumonia in two (22%).

Conclusion: The majorities of the initial manifestations of anti-NMDAR encephalitis in the Thai patients were seizures and psychiatric symptoms. The first episode of seizure without other neurological abnormalities especially among young adult women may reveal anti-NMDAR encephalitis. CRION may precede such an encephalitis. Leptomeningeal enhancement, with or without intraparenchymal lesion, may be more frequently seen in Thai patients.

Keywords: Anti-NMDAR encephalitis, Thai, Seizure, Leptomeningeal enhancement, CRION, Recurrent optic neuritis

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Anti-N-methyl-D-aspartate receptor [NMDAR] encephalitis is an autoimmune encephalitis presenting predominately in females, especially in young adults and children, with a unique combination of encephalitis and teratoma[1-4]. After the anti-NMDAR antibody was first discovered and reported by Dalmau et al in 2007[5], the paradigm for diagnosis, investigation, and treatment of acute to subacute encephalitis changed. However, physicians must suspect anti-NMDAR encephalitis to perform serological testing in order that early diagnosis and prompt treatment may result in better outcomes[6,7].

Correspondence to:

Jitprapaikulsan J. Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Lang Road, Bangkok 10700, Thailand.
Phone: +66-2-4197000, **Fax**: +66-2-4111103
Email: jiraporn.jit@mahidol.ac.th

Most reports describing anti-NMDAR encephalitis are from Western countries. They have reported a typical presentation involving the following sequence of clinical manifestations, prodromal symptoms, cognitive and psychiatric symptoms, behavioral changes, seizure, autonomic dysfunction, and hypoventilation[6,7]. Most studies have reported psychiatric symptoms to be the most common presentation[5,6]. However, presentations may differ in the Thai population, leading to a lack of recognition and timely management of the disease. Thus, we report the clinical manifestations, investigation findings, association with tumor, treatments, and outcomes for adult Thai patients diagnosed with anti-NMDAR encephalitis.

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Materials and Methods

This retrospective case series of Thai anti-NMDAR encephalitis patients was performed at the Department of Medicine, Siriraj Hospital, Bangkok, Thailand, between 2007 and 2016. Siriraj Hospital is the largest tertiary hospital in Thailand. The inclusion criteria were all patients older than 15 years of age who had clinical manifestations of encephalopathy and were positive for anti-NMDAR antibodies. The exclusion criterion was encephalopathies from other causes. The diagnosticians were board-certified neurologists.

The patients for our case series were identified retrospectively from the hospital's database, and their medical records were reviewed. Data on the clinical presentations, findings of the investigations, including the cerebrospinal fluid [CSF], brain imaging, and electroencephalogram [EEG] studies, the clinical courses, and the outcomes were collected. The definite diagnosis was determined by one positive anti-NMDAR antibody test in either the CSF or serum by the cell-based assay [CBA] method in patients presenting with the clinical syndromes of possible autoimmune encephalitis (namely, acute to subacute encephalopathy, cognitive impairment, psychotic disorders, seizures, and abnormal movements). This study was approved by Siriraj Institutional Review Board (reference: 738/2559).

Antibodies testing

The CSF and serum of the first patient from the year 2007 were sent to Oxford University. The test was graciously performed with a sensitive CBA by Professor Angela Vincent at the Oxford Neuroimmunology Laboratory.

The serum and CSF from other seven cases were sent to Prasat Neurological Institute, Bangkok, Thailand. They were screened by tissue immunohistochemistry, and confirmed by CBA on the EUROIMMUN AG BIOCHIP (Germany)[6]. The assignment of a positive or negative test result was decided by the intensity of the surface immunofluorescence of the transfected cells compared with the non-transfected cells. This method, indirect immunofluorescence using specific transfected cells, was also used to detect antibodies against α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid [AMPA] receptors, contactin-associated protein 2 [CASPR2], γ-amino-butyric acid receptors [GABAR], and leucine-rich glioma inactivated protein 1 [LGI1].

The antibody testing for case number 4 was performed at Siriraj Hospital by CBA (EUROIMMUN, Lübeck, Germany).

Results

Nine adult Thai patients, who were diagnosed as having anti-NMDAR encephalitis between 2007 and 2016, were identified. Their clinical characteristics are summarized at Table 1.

Clinical manifestations

Of the nine anti-NMDAR encephalitis patients, three (33%) developed typical prodromal symptoms, including fever, malaise, headache, nausea, vomiting, and diarrhea. The most common initial presentations were cognitive and psychiatric symptoms such as memory problems, mood disturbance, and hallucinations, as well as behavioral and personality changes in four patients (44%), seizure in four patients (44%), and cognitive impairment in only one patient (11%). During the clinical course, eight patients (89%) developed seizures, of which four (50%) had generalized tonic clonic seizures, and four (50%) had partial complex seizures. One patient (case number 5) developed status epilepticus within a week of initially having generalized tonic clonic seizures.

Abnormal movements were subsequently seen in eight patients (89%) during the clinical course of the disease. Of the eight patients, five (63%) had stereotypic movement, while six (75%) had dystonia and orofacial dyskinesia. In addition, one patient (13%) had choreoathetoid movement, one (13%) had myoclonus, and one (13%) had bruxism. None of the patients had abnormal movements as their first manifestation.

Five of the nine anti-NMDAR encephalitis patients (56%) developed autonomic instability such as cardiac dysrhythmia, unstable blood pressure, and hyperthermia and/or hypothermia.

Laboratory investigation

CSF analyses were performed on all patients. Six of the nine anti-NMDAR encephalitis patients (67%) had lymphocytic pleocytosis, and three (33.3%) had increased protein concentration. Nevertheless, three patients (33%) had normal CSF profiles. Viral polymerase chain reaction [PCR] of CSF for herpes simplex [HSV] type 1 was tested in all patients, and all results were negative.

Brain imaging was done on all patients, either by computed topography [CT] with contrast, or magnetic resonance imaging [MRI], or both. Only two out of the seven patients (29%) who had been given an MRI scan had T2 hyperintense signal at the hippocampus. Other areas of abnormalities were the right frontal lobe and the left corpus callosum. The imaging revealed

Table 1. Clinical features of adult patients with Anti-NMDAR encephalitis

	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	Total, n (%)
Sex	Female	Female	Female	Female	Female	Female	Female	Female	Male	Female 8 (89)
Age (years)	15	16	19	19	21	25	27	36	49	Median 21
Clinical manifestations										
Prodromal symptoms	No	No	No	No	Yes	No	Yes	No	Yes	3 (33)
Initial presenting symptoms	Seizure	Seizure	Psychiatric symptom	Seizure	Psychiatric symptom and cognitive impairment	Psychiatric symptom	Seizure	Psychiatric symptom and cognitive impairment	Cognitive impairment only	-
Seizure types	GTCS	Partial complex	GTCS	Partial complex	GTCS, SE	No	GTCS	Partial complex	Partial complex	8 (89)
Abnormal movement	Dystonia, orofacial dyskinesia, and choreoathetoid movement	Orofacial dyskinesia, stereotypic movement, and myoclonus	Dystonia, orofacial dyskinesia, and stereotypic movement	Stereotypic movement	Dystonia, orofacial dyskinesia, and stereotypic movement	Dystonia and stereotypic movement	Dystonia and orofacial dyskinesia	No	Bruxism, dystonia, and orofacial dyskinesia	8 (89)
Autonomic instability	Yes	No	No	No	Yes	Yes	No	Yes	Yes	5 (56)
Mechanical ventilation	Yes	No	No	No	Yes	Yes	No	No	Yes	4 (44)
Laboratory investigations										
EEG	Slow activity	Slow activity	Slow activity	Slow activity	Slow activity and extreme delta brush	Slow activity	Normal	Temporal epileptic foci	Slow activity	8 (89)
LP before imaging (days)	NA	–8	NA	–1	NA	+1	NA	NA	+5	-
Abnormal CT brain with contrast	Not done	No	Not done	No	No	No	No	Leptomeningeal enhancement	No	1/7 (14)
Location of abnormal MRI scan of the brain	Right frontal lobe	Right temporal lobe	Left corpus callosum	Not done	Not done	Both hippocampal areas	No	Leptomeningeal enhancement	Leptomeningeal enhancement	6/7 (86)
CSF										
Date to perform LP from onset (days)	17	14	23	25	13	8	20	10	5	Range 5 to 25
Cell count (mm^3)	WBC 10, L 99%	WBC 20, L 100%	WBC 1, L 100%	WBC 4, L 99%	WBC 248, L 99%	WBC 8, L 100%	WBC 3, L 96%	WBC 14, L 94%	WBC 162, L 67%	-
Protein (mg/dL)	19	24	27	32	57	24	21	69	53	Range 19 to 69
Glucose (CSF/Blood) (mg/dL)	67/84	65/100	61/86	84/124	57/92	65/127	61/108	65/96	63/122	Mean ratio 0.63
PCR for microbial	HSV, JEV- negative	HSV, JEV, MTB, NTM- negative	HSV- negative	HSV, JEV, EV- negative	HSV- negative	HSV, EBV, CMV, VZV- negative	HSV, JEV, EBV, CMV, VZV- negative	HSV, JEV, EBV, CMV, VZV, HHV-6, MTB- negative	HSV, EBV, CMV, VZV- negative	-
Tumor (procedure to investigate)	Right ovarian teratoma (by CT)	No (by CT)	No (by CT)	No (by ultrasound)	Bilateral ovarian teratoma (by CT)	Right ovarian cyst (transvaginal ultrasound)	Right ovarian teratoma (by CT)	No (by CT)	Not done	3 (33)
Treatments										
Tumor resection	Yes (previous)	No	No	No	Yes	No	Yes	No	No	3 (33)
Duration from onset to treatment (IVMP) (days)	30	10	24	26	17	10	22	11	51 (plasma exchange)	Range 10 to 30
Immunotherapy										
Corticosteroids	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8 (89)
Intravenous immunoglobulin	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	6 (67)
Plasma exchange	No	No	No	No	Yes	No	No	No	Yes	2 (22)
Rituximab	No	No	Yes	No	No	No	No	No	No	1 (11)
Azathioprine	No	No	No	Yes	No	No	No	No	No	1 (11)
Neuroleptic medications	Quetiapine	Haloperidol	Risperidone	Risperidone	No	Olanzapine and haloperidol	No	Haloperidol	Haloperidol	7 (78)
LOS at Siriraj Hospital (days)	85	21	56	11	34	35	36	19	63	Range 11 to 85
Outcomes										
Recovery	Marked	Partial	Partial	Partial	No	Marked	Marked	Partial	No	-
Sequelae	No	Psychiatric symptom	Psychiatric symptom, speech disturbance and partial dependency	Psychiatric symptom, speech disturbance and partial dependency	Death (VAP)	Speech disturbance	No	Memory deficit	Death (VAP)	-
Latest follow-up (months)	85	40	6	38	No follow-up due to death	Lost to follow-up	13	34	No follow-up due to death	Range 6 to 85
Latest outcome	Improved	Improved	Speech disturbance and partial dependency	Relapse at 36 months during pregnancy and partial dependency	-	-	Improved	Improved	-	-

CMV = cytomegalovirus; CSF = cerebrospinal fluid; CT = computed topography; EBV = Epstein-Barr virus; EEG = electroencephalography; GTCS = generalized tonic clonic seizure; HHV = human herpes virus; HSV = herpes simplex virus; IVMP = intravenous methylprednisolone; JEV = Japanese encephalitis virus; L = lymphocyte; LOS = length of stay; MRI = magnetic resonance imaging; MTB = Mycobacterium tuberculosis; NA = data not available; NTM = non-tuberculous Mycobacterium; SE = status epilepticus; VAP = ventilator-associated pneumonia; VZV = varicella zoster virus; WBC = white blood cell

+ indicated LP was done before imaging whereas – indicated imaging was done before LP

leptomeningeal enhancement in two patients (22%), who had fever and headache without nuchal rigidity.

In addition, all nine patients had EEGs either routinely or as part of monitoring. Seven patients (78%) had continuous slow activities, and one (11%) had temporal lobe epileptic foci. The EEG characteristic of anti-NMDAR encephalitis, which is an extreme delta brush appearance, was found in one patient (11%).

Case number 5 had status epilepticus in the referring hospital and seizure termination with five intravenous antiepileptic medications (namely, phenytoin, sodium valproate, levetiracetam, phenobarbital, and midazolam). The case was referred to Siriraj Hospital where the EEG was performed. This patient did not have EEG seizure activities; however, she did have diffuse slow activity and extreme delta brush on her EEG recording while EEG monitoring was being performed at Siriraj Hospital.

Disease associations

Due to the well-recognized association between anti-NMDAR encephalitis and ovarian teratoma, six of the nine patients (67%) underwent CT abdomen and pelvic imaging. Three patients (33%) did not have such an imaging performed because of hemodynamic instability. Three of the six patients (50%) had an ovarian teratoma including two unilateral and one bilateral.

None of the patients had positron emission tomography performed because the Thai Universal Coverage Scheme does not cover this imaging modality for this disease entity, and the patients could not personally afford it. No other autoimmune diseases or oncologic associations were found by history, physical examinations, laboratory findings, or the available imaging.

Treatment and outcomes

All nine anti-NMDAR encephalitis patients received immunotherapy where five patients (56%) received a combination of methylprednisolone and intravenous immunoglobulin [IVIG], one (11%) was treated with corticosteroids alone or 1 gram of methylprednisolone once a day, as specified, one (11%) was treated with plasma exchange alone, one (11%) was treated with a combination of intravenous methyprednisolone and plasma exchange, and one refractory case (11%) was given a triple therapy of IVIG, methylprednisolone, and rituximab.

Neuroleptic medications for controlling psychiatric symptoms and abnormal movements were administrated to seven out of the nine patients (78%) during admission.

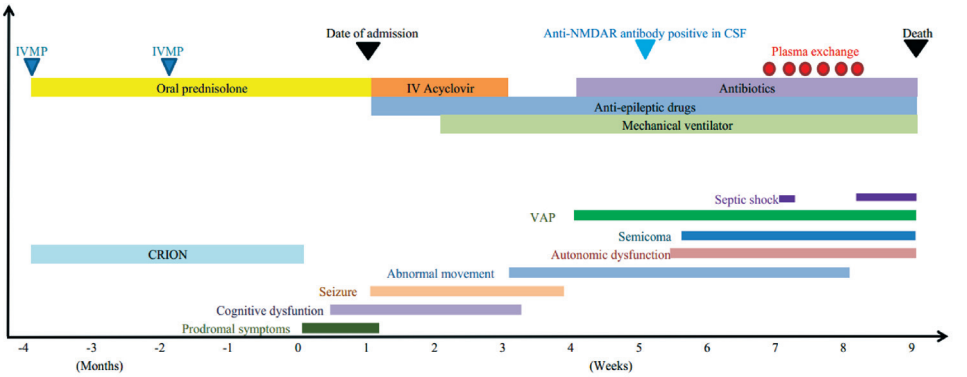
All three patients with an ovarian teratoma underwent a complete tumor resection with pathological confirmation. Two of those patients were markedly improved at 13 and 85 months of follow-up, while the third died from hospital-acquired pneumonia.

The median length of the hospital stays was 35 days (range 11 to 85). After the immunotherapy treatment, one anti-NMDAR encephalitis patient (11%) had a marked recovery with the immunotherapy alone, four (44%) had a partial recovery, and two (22%) died from ventilator-associated pneumonia without neurological improvement after receiving methylprednisolone and plasma exchange. With reference to Table 1, a "marked improvement" was defined as a reduction in the modified Rankin Scale of 2 or more, whereas a "partial recovery" was defined as a 1-score improvement.

One patient who was administered methylprednisolone and IVIG was lost-to-follow-up because her family sought alternative treatment in keeping with their superstitious beliefs about the causality of her condition. After treatment with methylprednisolone and IVIG, this patient regained consciousness, the autonomic instability and stereotypic movement disappeared, and ventilator support was discontinued. However, she still had psychomotor retardation before discharge.

Of the six patients who could be followed-up, four patients (67%) had continuously improved, having the ability to do daily life activities. Nevertheless, two patients (33%) still had speech disturbance, and were partially dependent. One patient (11%) had relapse during unplanned pregnancy at 36 months after treatment (case number 4).

Figure 1 shows the timeline of the disease course of case number 9. This case was selected because he was the only late-adult male patient and because he had a rare prior condition, which was chronic relapsing inflammatory optic neuropathy [CRION]. The clinical outcome of this case was death. Four months prior to admission, he developed subacute bilateral painful visual loss with optic disc swelling within seven days. An MRI orbit illustrated gadolinium enhancement of both optic nerves, with more on the right side. Serum aquaporin-4 [AQP-4] immunoglobulin [IgG] was negative by CBA. He was given intravenous methylprednisolone for three days and had a rapid improvement. While tapering off oral prednisolone around two months later, he had a worsening visual loss of the left eye. He subsequently received a further high dose of methylprednisolone as well as oral prednisolone (again,



CRION, chronic relapsing inflammatory optic neuropathy; CSF, cerebrospinal fluid; IVMP, intravenous methylprednisolone; NMDAR, N-methyl-D-aspartate receptor; VAP, ventilator-associated pneumonia

Figure 1. Timeline illustrating clinical presentation, treatment and complications of patient case number 8, CRION with Anti-NMDAR encephalitis.

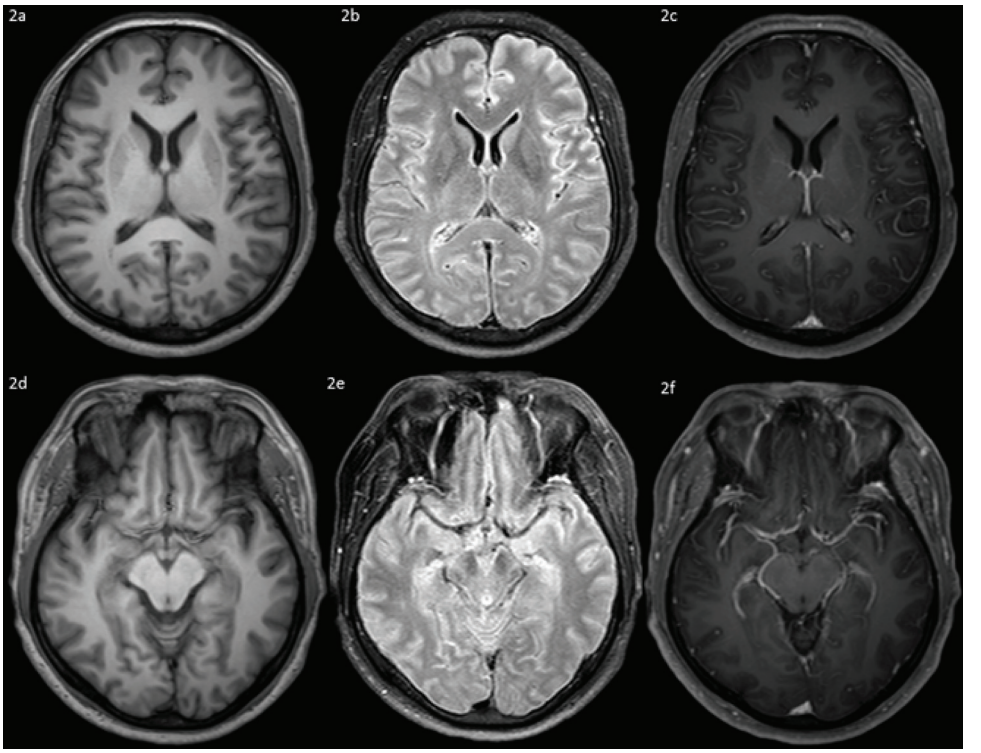


Figure 2. Brain MRI with Gadolinium (Gd) demonstrates diffuse leptomeningeal enhancement in T1W image with Gd (2c, 2f) without temporal lobes and intraparenchymal abnormalities in T1W (2a, 2d) and T2W FLAIR image (2b, 2e).

slowly tapered off over two months). Just after discontinuing the oral prednisolone, he developed subacute encephalopathy and seizures, for which he was hospitalized. A brain MRI (Figure 2) revealed leptomeningeal enhancement without intraparenchymal abnormalities. The venereal disease research laboratory [VDRL] and viral PCRs for HSV, varicella-zoster virus, Epstein-Barr virus, and cytomegalovirus were negative in the CSF. Acyclovir was given as empirical treatment. Typical abnormal movements finally developed during the clinical course of the disease, raising the suspicion of a diagnosis of anti-NMDAR encephalitis. A consequent anti-NMDAR antibody CBA test of the CSF was positive. This patient was not treated with

methylprednisolone due to severe infection, but plasma exchange was done two weeks after the diagnosis due to hemodynamic instability. A CT chest and whole abdomen scan was scheduled to demonstrate any tumors. Unfortunately, the patient died from ventilator-associated pneumonia and sepsis before the CT could be performed.

Discussion

The anti-NMDAR encephalitis patients diagnosed at Siriraj Hospital, Bangkok, Thailand, had certain manifestations that differed from previous reports. The typical prodromal symptoms were found in only three out of the nine (33%) confirmed anti-NMDAR patients. Seizure without other preceding neurological signs and symptoms was the first presentation in nearly half of our patients. One patient had CRION, which had never been reported as preceding anti-NMDAR encephalitis. Atypical imaging, namely, leptomeningeal enhancement, was described for 22% of the cases in this series.

The authors found that one-third of the cases in our study had reported prodromal symptoms (Table 2). This is a lower prevalence than in the case series of Dalmau et al, which reported a figure of 70%[6]. To date, no exact cause of prodromal symptoms has been discovered, so we cannot explain the difference. However, we suggest that clinicians should be aware that neurological symptoms without prodromal syndrome may be common with anti-NMDAR encephalitis.

Similar to other reports, the present study found that cognitive impairment and psychiatric symptoms also commonly presented as initial manifestations (50% to 67%), which led to the misdiagnosis of a psychiatric condition, such as psychosis, in some cases[6-8]. The manifestation of such symptoms is hypothesized to relate to the dysfunction of the temporal and frontal lobes, in which NMDA receptors are abundant.

The distinctive finding of this study is that seizure was the first manifestation in 44% of cases, whereas other studies have reported 16.6% to 27.6%[9,10]. Subsequent features suggestive of immune-mediated encephalitis occurred within a few days of the seizure. Therefore, a lack of awareness of seizure as the initial presentation of this rare disease may lead to a delayed diagnosis in patients presenting with seizure alone.

A previous Thai study in 2013[11] reported five cases of anti-NMDAR encephalitis. Three patients presented with a combination of psychosis and seizure, and one patient had an initial presentation of seizure with the concomitant presence of NMDAR antibodies and anti-neuronal nuclear antibodies.

Seizure has been reported more frequently as the initial presentation in males than females. In the literature, the largest series (577 cases) demonstrated that more men presented with seizure (14/52, 27%) than women (35/313, 11%, $p = 0.007$)[12]. Furthermore, one study demonstrated that seizure was significantly

Table 2. Previous reports and present report of the characteristics of anti-NMDAR encephalitis

	Number of patients (% female)	Median age (range)	Prodromal symptoms	Seizure as initial presentation	Psychiatric symptoms as initial presentation	Abnormal EEG finding	Ovarian teratoma in female (%)	Markedly recovered at latest follow-up	Mortality
Present report	9 (88.9)	21 (15 to 49)	3 (33.3)	4 (44.4)	4 (44.4)	8 (88.9)	3/7[a] (42.9)	4/7[a] (57.0)	2/7[a] (28.0)
Dalmau et al. 2007[5]	12 (100)	27 (14 to 44)	10 (10.0)	Not specified	Not specified	Not specified	12/12[b] (100)	7 (58.3)	3 (25.0)
Dalmau et al. 2008[6]	100 (91.0)	23 (5 to 76)	72/84[c] (85.7)	23[d] (23.0)	77 (77.0)	92/92[e] (100)	58/98[f] (59.2)	47 (47.0)	7 (7.0)
Saraya et al. 2013[11]	5 (80.0)	39 (5 to 43)	3 (60.0)	3[g] (60.0)	4[h] (80.0)	Not specified	1/4 (25.0)	1 (20.0)	0 (0.0)
Lin et al. 2014[9]	12 (83.3)	18 (7 to 28)	7 (83.3)	2[i] (16.6)	10 (83.3)	11 (91.7)	3/10 (30.0)	6 (50.0)	0/11[j] (0.0)
Chi et al. 2016[14]	96 (62.5)	24.5 (9 to 71)	Not specified	Not specified	Not specified	61/82 (73.6)	Not specified	Not specified	11/96 (11.5)
Huang et al. 2016[10]	29 (51.7)	7.7±3.02 and 28.3±11.12[k]	7 (24.1)	8 (27.6)	18 (62.1)	28 (97.0)	Not specified	Not specified	Not specified

[a] Information was available for 7 patients.

[b] The study was described as teratoma.

[c] Information was available for 84 patients.

[d] The study was described as neuropsychiatric symptoms.

[e] Information was available for 92 patients.

[f] Information was available for 93 patients. The study was described as tumor, which consisted of 53 female patients with ovarian teratoma, 1 female with sex-cord stromal tumor, 1 female with neuroendocrine tumor, and another female with teratoma of the mediastinum. There was one male with immature teratoma of the testis, and another male with small cell lung cancer.

[g] The study was described as psychosis and seizure.

[h] The study was described as 3 patients with psychosis and seizure, and one with behavior change.

[i] The study was described as neurological symptoms.

[j] One patient was lost to follow-up.

[k] The average ages of children (number = 15) and adults (number = 14) were 7.7±3.02 and 28.3±11.12 years, respectively.

more common as the first manifestation in eight out of 12 (67%) males versus eight out of 58 (16%) females ($p<0.001$)[13]. The explanation might be a lack of recognition and delayed diagnosis in the case of men rather than a hormonal effect[12]. The difference between our findings and those of previous studies in terms of the first manifestation of seizure and gender might be due to differences in the genetic predispositions of the study populations, or because of the relatively small sample size in our study compared with some of the previous studies. However, our finding raises awareness of the diagnosis of anti-NMDAR encephalitis in the clinical context of first onset seizure, particularly among young adult woman, even without other neurological deficits.

During the course of the disease, 89% of our patients ultimately developed seizure; this is similar to previous studies that found most patients (76% to 84%) had seizures. The most common type of seizure reported for this disease is generalized tonic clonic seizure[5,6,8]. Status epilepticus was found in 11% of cases in our study. Prior reports have revealed a variety of prevalence of status epilepticus (9.8% to 39.2%)[8,14].

The present study includes an interesting CRION patient who developed anti-NMDAR encephalitis. The early course of the disease was consistent with CRION, so corticosteroid was given as the definitive treatment[15]. To the best of our knowledge, no previous research has identified an association between CRION and anti-NMDAR encephalitis. We are unable to explain this association; however, one plausible explanation might be the concomitant presence of anti-NMDAR antibody and other antibodies attributed to optic neuritis. Previous studies have reported co-existing anti-NMDAR encephalitis and neuromyelitis optica spectrum disorder[16-18]. One patient had clinical manifestations of anti-NMDAR encephalitis and then developed optic neuritis 10 months later. He also had positivity for anti-NMDAR antibodies in the first event, and for AQP-4 IgG in a subsequent optic neuritis[18]. There were four case reports of optic neuritis in anti-NMDAR encephalitis that did not have AQP-4 IgG positivity[19-22]. However, one of those had concomitant anti-myelin oligodendrocyte glycoprotein [MOG] antibody[19]. Recently, anti-MOG presenting with CRION has been described as well[23]. The patient might have anti-MOG disease because he had certain features of such a disease by having simultaneous bilateral eyes involvement, optic disc swelling, and steroid responsiveness. However, this antibody test was not available when we were treating this patient.

Abnormal movements were also common symptoms among our patients and in a previous study[6], with a prevalence of 89% and 86%, respectively. Similar to previous studies, dystonia, stereotypic movements, and orofacial dyskinesia were frequent types of abnormal movements found in our case series[6,9]. None of our patients presented with abnormal movements. The mechanism of these symptoms is still unknown, but dysfunction of the basal ganglion has been proposed as a possible explanation[24].

Autonomic dysfunction is characterized by cardiac dysrhythmia, hypertension, hypotension, and hyperthermia or hypothermia. There were no distinctive differences in the proportion of the dysfunction found in our study (56%) and prior studies (28% to 83.3%)[6,8,9].

EEG of this disorder is usually compatible with slow activity, while a small number of patients may develop epileptic activities. Recently, a peculiar pattern of extreme delta brush has been described in approximately 33% of patients with anti-NMDAR encephalitis[25,26]. The present study also revealed a small percentage with this pattern (11%). Although only a small proportion of patients have this pattern, such a noticeable pattern may help clinicians in the diagnosis and early treatment of this type of encephalitis while serology is pending.

In the brain imaging studies of Dalmau et al, about half of the patients had MRI-scan abnormalities located in the medial temporal lobes and cerebral cortex, while 16% of patients had lesions at cerebellum, brainstem, basal ganglion, and meninges[6]. A normal CT and MRI scan was unable to distinguish anti-NMDAR encephalitis from other diseases, which was seen in one out of seven patients in our series, and this patient had normal CSF findings. Although leptomeningeal enhancement has rarely been reported[27], our study demonstrated two patients with this finding by brain imaging. The plausible etiology of the leptomeningeal enhancement would be a co-existing antibody with an anti-NMDA receptor. Glial fibrillary acidic protein [GFAP]-IgG has recently been reported as a novel autoantibody of meningoencephalitis. There was also 15% dual positivity of GFAP and NMDA antibodies[28,29]. However, we did not perform GFAP antibody testing because, in both cases, the clinical syndrome of GFAP autoimmunity had not been established at the time of diagnosis.

Previous studies have reported that more than 80% of patients had an abnormal CSF profile[6,30], which was characterized by lymphocytic pleocytosis and increased protein concentration. Notably, a normal

CSF examination was found in this autoimmune encephalitis[30]. Likewise, we found 33% of patients had a normal CSF analysis. This is compatible with two previous studies that have reported a prevalence of a normal CSF analysis in anti-NMDAR encephalitis of 5% and 37%[6,8].

The prognosis of this disorder in a previous cohort of 360 patients found that 75% were markedly recovered. The others had severe deficits that affected daily life or died. In our report, 67% of the patients experienced marked recovery[7,31].

The present study has limitations. The incompleteness of the investigation, particularly the lack of advanced imaging to search for tumors, may have flawed the identification of tumors. The small number of patients may also have hampered the ability to estimate the true prevalence of features of this disease among Thai patients with anti-NMDAR encephalitis.

Conclusion

Anti-NMDAR encephalitis manifests from seizure-only to fulminant encephalopathy. In adult patients initially presenting with a seizure without prodromal or psychiatric symptoms, anti-NMDAR encephalitis should be considered in the differential diagnosis. CRION patient may precede anti-NMDAR encephalitis. Leptomeningeal involvement, with or without intraparenchymal lesion, can be been found in this condition among Thai patients.

What is already known on this topic?

Anti-NMDAR encephalitis is an autoimmune disease commonly associated with OT and for which the antibody was discovered in 2007. This disorder is usually found in young adult females. Diagnosis is based on typical clinical manifestations, seizure, psychiatric, or abnormal movements, physical examinations, and laboratory investigations (including EEG, CSF analysis, antibody testing, and brain imaging). Tumor resection and immunotherapy are considered as the first-line treatment.

What this study adds?

The present study showed seizure is a more common presentation among Thai patients with anti-NMDAR encephalitis. The first episode of seizure (especially among young adult woman) without other neurological symptoms may reveal anti-NMDAR encephalitis. Leptomeningeal enhancement is a rare pattern from brain imaging, but it was found to be more common among Thai patients. CRION may also be associated with anti-NMDAR encephalitis due to concomitant antibodies.

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Potential conflicts of interest

The authors declare no conflict of interest.

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