

Original article

# Clinical manifestations, treatment outcomes, and prognostic factors of pediatric anti-NMDAR encephalitis in tertiary care hospitals: A multicenter retrospective/prospective cohort study

Napa Pruetarat<sup>a</sup>, Wiracha Netbaramee<sup>b</sup>, Siriporn Pattharathitikul<sup>c</sup>  
Montida Veeravigrom<sup>a,d,\*</sup>

<sup>a</sup> Department of Pediatrics, King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Thailand

<sup>b</sup> Department of Pediatrics, Chonburi Hospital, Chonburi, Thailand

<sup>c</sup> Department of Pediatrics, Prapokklao Hospital, Chanthaburi, Thailand

<sup>d</sup> Division of Neurology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

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## Abstract

**Objective:** Anti-NMDAR encephalitis is an acute autoimmune neurological disorder that is increasingly recognized in pediatric populations. Several studies of the disorder have been conducted worldwide but there are few publications in Thailand. Here, we describe the clinical manifestations, treatment outcomes, and prognostic factors in children with anti-NMDAR encephalitis.

**Methods:** Between January 2007 and September 2017, we conducted a retrospective/prospective cohort study of children diagnosed with anti-NMDAR encephalitis from three tertiary care hospitals in Thailand: King Chulalongkorn Memorial Hospital, Chonburi Hospital, and Prapokklao Hospital. We assessed the Modified Rankin Score (mRS) score for each participant to measure severity of disease and treatment outcome at baseline, 12, and 24 months.

**Results:** We recruited 14 participants (1–13 years with median age 8.4 years). Participants were followed up for a median of 20.5 months. Clinical manifestations included behavioral dysfunction (100%), movement disorder (93%), speech disorder (79%), sleep disorder (79%), and seizures (79%). All patients received first-line immunotherapy (corticosteroids: 100%, intravenous immunoglobulin: 79%, plasma exchange: 21%). Second-line immunotherapy (cyclophosphamide) was administered to 57% of patients. During the first 12 months, 8 patients (62%) achieved a good outcome (mRS  $\leq 2$ ). At 24 months, 9 patients (81%) had achieved a good outcome. Altered consciousness and central hypoventilation were predictors of poor outcome. ( $p < 0.05$ ).

**Conclusions:** We observed similar clinical manifestation of anti-NMDAR encephalitis in Thai children to those reported in other countries. Furthermore, the percentage of patients with good outcomes in our study was comparable with previous studies. Further studies are required to investigate other populations in other regions of Thailand.

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**Keywords:** Pediatric encephalitis; NMDAR; Autoimmune encephalitis

## 1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an acute autoimmune disorder first described in 2007 [1]. The disease was first observed in

\* Corresponding author. MD 1873 Rama IV Road, Pratumwan, Bangkok 10330, Thailand. Tel.: +66 22565275.

E-mail address: [vmontida@hotmail.com](mailto:vmontida@hotmail.com) (M. Veeravigrom).

women with ovarian teratoma [2], then the diagnosis was subsequently widened to include female patients without cancer, male patients, and children.

Anti-NMDAR encephalitis is the most common cause of autoimmune encephalitis in children [3] and many international literature reviews have been conducted regarding this disease in children. The disorder manifests with flu-like symptoms that progress to psychiatric symptoms, dyskinesia, and cognitive decline [1]. Anti-NMDAR encephalitis in children has different symptom presentations and associations with tumors than does the disease in adults [4–6]. Compared with adult patients, children more often have seizures at first presentation. Abnormal movements, particularly limb dystonia, also present more frequently in children [7].

Anti-NMDAR encephalitis is diagnosed by the detection of NMDA receptor autoantibodies in cerebrospinal fluid (CSF) [8]. If a tumor, such as an ovarian tumor, underlies the disease, the tumor must first be removed. Subsequently, treatment with immunotherapy is administered in two steps. First-line immunotherapy consists of steroids, intravenous immunoglobulin, and plasmapheresis, while second-line immunotherapy comprises medications such as rituximab and cyclophosphamide. These treatments are discontinued once patients show substantial improvement [6–7].

Several studies of anti-NMDAR encephalitis have been conducted worldwide. However, there are few publications regarding pediatric anti-NMDAR encephalitis in Thailand. Therefore, we aimed to study pediatric anti-NMDAR encephalitis in Thailand, assessing clinical manifestation, treatment outcomes, and prognostic factors.

## 2. Materials and methods

### 2.1. Patients

Between January 2007 and September 2017, we recruited 14 patients (7 from King Chulalongkorn Memorial Hospital, 5 from Chonburi Hospital, and 2 from Prapokklao Hospital) with anti-NMDAR encephalitis who were positive for NMDAR autoantibodies in the CSF. Eighty-one patients were tested for NMDAR antibodies. (48 from King Chulalongkorn Memorial Hospital, 23 from Chonburi Hospital, and 10 from Prapokklao Hospital) We conducted a retrospective/prospective cohort study, collecting data at the time of diagnosis, and 12 and 24 months after treatment. The study protocol was approved by the Chulalongkorn Institutional Review Board (IRB).

### 2.2. Outcome measurements

We assessed the Modified Rankin Score (mRS) (Table 1) to measure severity of disease and treatment outcome for each participant [9].

### 2.3. Statistical analysis

All statistical analyses were conducted with IBM SPSS statistics, version 22 (IBM Corp: Armonk, NY). We compared categorical variables with the Chi-square test, while continuous variables were compared with independent t-tests. In the univariate analysis, we compared baseline characteristics with treatment outcome.

## 3. Results

During the study period, we recruited 14 patients with anti-NMDAR encephalitis (male:  $n = 4$ , female:  $n = 10$ ). Patients had a median age of 8.4 years, with a range from 1 to 13 years in boys and 2–13 years in girls. Patients were followed up for a median of 20.5 months, with a mean duration of hospitalization of 54.9 days, ranging from 4 to 150 days. During the study, 50% of patients were admitted to the intensive care unit (ICU) because of refractory status epilepticus and supported by a ventilator (25% of boys and 60% of girls) (Table 2).

### 3.1. Clinical manifestations

The most common symptoms we observed were behavioral dysfunction (100%) followed by movement disorder (93%), speech disorder (79%), sleep disorder (79%), seizures (79%), prodromal symptoms (71%), memory deficit (36%), psychiatric symptoms (29%), and autonomic dysfunction (14%). The most common prodromal symptom was fever (71%) and the most common movement disorder was oropharyngeal dyskinesia (79%) (Fig. 1). The initial clinical presentation was behavioral change (42%), seizure (35.7%), Sleep disturbance (7%), oropharyngeal dyskinesia (7%), respectively. Sleep disturbances, memory deficits, psychiatric symptoms, oropharyngeal dyskinesia, and chorea were more common in girls than in boys. Our 1-year-old male patient developed anti-NMDAR encephalitis after Herpes simplex virus type II encephalitis with hypodensity lesions in bilateral temporal-occipital area. (For details of individual cases, please refer to [supplementary Table 1](#)).

We observed positive results for NMDAR autoantibodies in the CSF of 100% of patients and in the serum of 71% of patients. Brain imaging did not demonstrate any specific findings. Only one patient's MRI scan demonstrated leptomeningeal enhancement. Electroencephalograms showed epileptic or encephalopathy patterns, while an extreme delta brush was observed in 50% of patients.

### 3.2. Treatment outcome

The outcome study was completed by 13 patients at 12 months and 11 patients at 24 months. Most patients

Table 1  
Modified Rankin Scale [13].

0. No symptoms
1. No significant disability. Able to carry out all usual activities despite some symptoms
2. Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3. Moderate disability. Requires some help, but able to walk unassisted.
4. Moderately severe disability. Unable to attend to own body needs without assistance and unable to walk unassisted.
5. Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6. Dead

Table 2  
Overview of age, duration of hospitalization, ICU admission, and use of ventilator support among patients.

	Total (n = 14)	Male (n = 4)	Female (n = 10)	p value
Age (years), median (range)	8.4 (2–13)	10.2 (5–13)	7.7 (2–13)	0.24
Duration of hospitalization (days), Median (range)	54.9 (4–150)	54.2 (4–150)	55.2 (9–149)	0.97
ICU admission, n (%)	7 (50%)	1 (25%)	6 (60%)	0.55
On ventilator, n (%)	7 (50%)	1 (25%)	6 (60%)	0.55

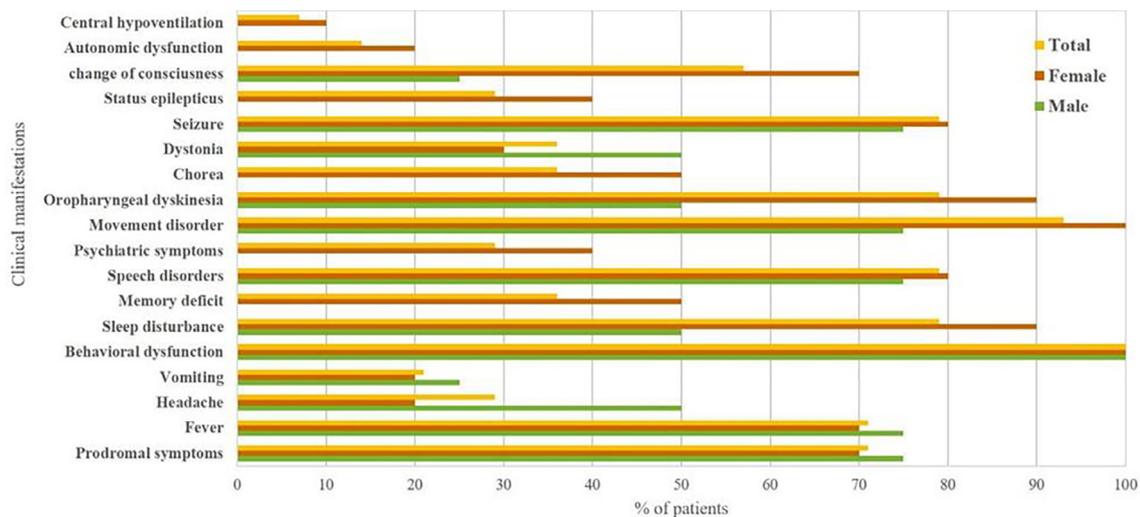


Fig. 1. Summary of clinical manifestations according to sex.

showed improved outcome after treatment (Fig. 2). However, there was 1 recently diagnosed patient (diagnosis received within the last 12 months), and 3 patients diagnosed within the last 24 months. These patients were not included in this report.

At baseline (before treatment), most patients had a mRS score of 5 (severe disability, 50%). After treatment at 12 and 24 months, the proportion of patients with good mRS scores increased, with approximately 30% at 12 months and 60% at 24 months having an mRS score of 1.

All patients received first-line immunotherapy (corticosteroids: 100%, intravenous immunoglobulin: 79%, and plasma exchange: 21%). Second-line immunotherapy (cyclophosphamide) was administered to 57% of patients. During the first 12 months, 8 patients (62%)

achieved a good outcome (mRS  $\leq 2$ ). At 24 months, 9 patients (81%) achieved a good outcome (Table 3).

### 3.3. Factors associated with outcome

Our data showed that good outcome was more common in older patients than in younger patients. Furthermore, duration of hospitalization was longer in those in the poor outcome group. A short time to treatment was associated with a better outcome (Table 4). Boys more often had a good outcome than did girls, with 100% of boys and 50% of girls showing a good outcome after treatment at 12 months. A good baseline mRS score appeared to predict good outcome. For those with a poor outcome at 12 months, outcomes improved at 24-month follow-up (Table 5).

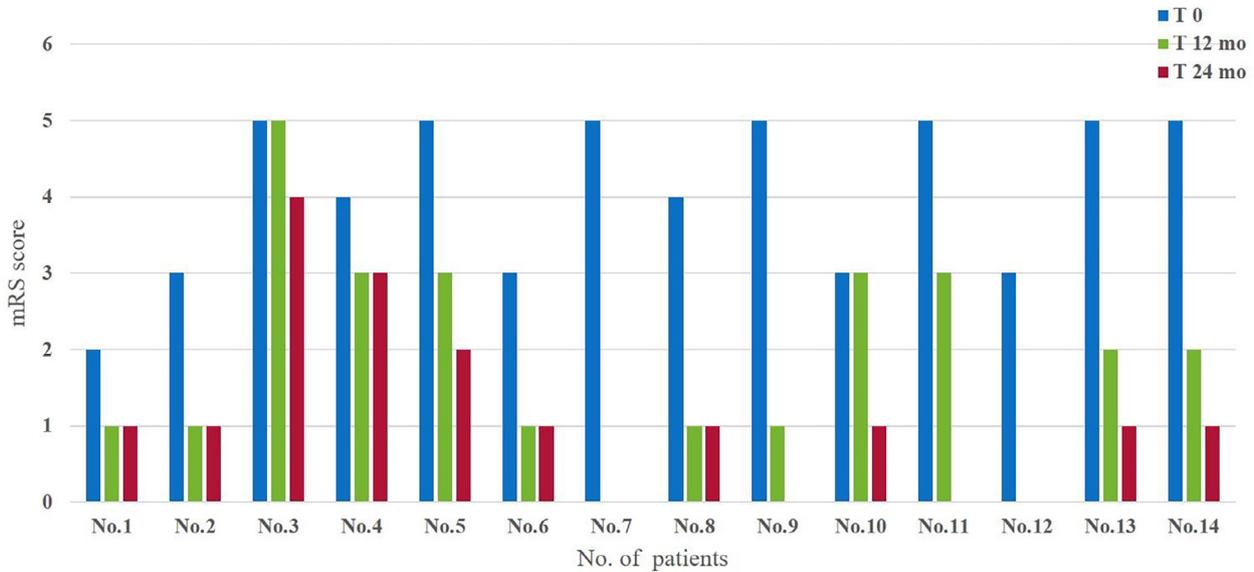


Fig. 2. Summary of treatment outcome represented by Modified Rankin Scale (mRS) scores at 12 and 24 months according to sex.

Table 3

Time to treatment and treatment types among all patients.

Treatment	n = 14
First-line treatment (Median time to first-line treatment)	100% (15 days)
Second-line treatment (Median time from first-line to second-line treatment)	57% (54 days)
<i>Type of first-line treatment</i>	
Corticosteroid	100%
Intravenous immunoglobulins	79%
Plasma exchange	21%
<i>Type of second-line treatment</i>	
Rituximab	0%
Cyclophosphamide	57%
<i>Good outcome</i>	
At 12 months	62%
At 24 months	81%

Table 4

Outcome according to age, duration of hospitalization, and time to treatment at 12 and 24 months.

	Outcome at 12 months			Outcome at 24 months		
	Good outcome (n = 8)	Poor outcome (n = 5)	P-value	Good outcome (n = 9)	Poor outcome (n = 2)	P-value
Age (years)	9.37 (SD 4.34)	6.6 (SD 1.67)	0.20	9.4 (SD 3.6)	7 (SD 1.4)	0.39
Duration of Hospitalization (days)	37.3 (SD 46.6)	88.2 (SD 40.1)	0.07	57.0 (SD 47.2)	93.5 (SD 78.4)	0.38
Time to treatment (days)	10.7 (SD 2.6)	16.8 (SD 6.4)	0.17	10.7 (SD 6.7)	17.0 (SD 12.7)	0.32

### 3.4. Prognosis factors

In the univariate analysis, we observed the statistically significant predictors of poor outcome which included altered consciousness ( $p < 0.05$ ) and central hypoventilation ( $p < 0.05$ ). (Table 6).

### 4. Discussion

Our study suggested that the presentation of anti-NMDAR encephalitis in children differs from that reported in adults. Adult patients usually present with acute behavioral change and psychosis followed by sei-

Table 5  
Outcome according to sex and baseline mRS score at 12 and 24 months.

	Outcome at 12 months			Outcome at 24 months		
	Good outcome (n = 8)	Poor outcome (n = 5)	P-value	Good outcome (n = 9)	Poor outcome (n = 2)	P-value
<i>Sex</i>						
Male	3	0	0.11	3	0	0.33
Female	5	5		6	2	
<i>Pre mRs</i>						
Good	1	0	0.41	1	0	0.62
Poor	7	5		8	2	

Table 6  
Factors associated with outcome in univariate analysis.

Variables	Unadjusted effects	Adjusted effect	95%CI
Age	0.003	–	–
Sex	0.317	–	–
Admit ICU	1.303*	0.589	–1.461, 2.640
<i>Clinical manifestations</i>			
Prodromal symptom	–0.098	–	–
Fever	–0.098	–	–
Headache	0.503	–	–
Vomiting	0.740	–	–
Behavioral dysfunction	–	–	–
Sleep disturbance	–0.881*	–1.272**	–2.368, –0.175
Memory deficit	–0.115	–	–
Speech disorder	0.537	–	–
Psychiatric symptom	–0.572	–	–
Movement disorder	1.052	–	–
Oropharyngeal dyskinesia	–0.315	–	–
Chorea	1.081*	–0.081	–1.272, 1.110
Dystonia	0.095	–	–
Seizure	0.325	–	–
Status epilepticus	0.971*	0.117	–1.196, 1.431
Altered consciousness	1.290**	0.888	–0.953, 2.729
Cardiac dysfunction	–	–	–
Autonomic dysfunction	0.028	–	–
Central hypoventilation	2.179**	1.556*	–0.186, 3.298
<i>Treatment</i>			
Methylprednisolone	–	–	–
IVIG	0.918*	0.745	–0.533, 2.024
Cyclophosphamide	0.307	–	–
Plasma exchange	0.740	–	–
<i>Treatment outcome</i>			
mRs 12 mo.	–1.857***	–1.857***	–2.532, –1.182
mRs 24 mo.	–2.435***	–2.476***	–3.190, –1.763

\* p < 0.25.

\*\* p < 0.05.

\*\*\* p < 0.01.

zures, dyskinesia, memory deficits, and autonomic dysfunction [1,11,12]. Our study showed that most children with anti-NMDAR encephalitis presented with behavioral dysfunction, movement disorder, speech disorder, sleep disorder, prodromal symptoms, and seizures. The most common prodromal symptom observed in our sample was fever, and the most common movement disorder was oropharyngeal dyskinesia. A recent study reported that seizures were more common in children

due to modification of hormonal activity related to puberty, which could represent a key factor in the progression of anti-NMDAR encephalitis at different ages [13–16]. The initial clinical presentation was behavioral change (42%), seizure (35.7%), Sleep disturbance (7%), oropharyngeal dyskinesia (7%) which was different from recent paper that seizure was the most common initial presentation in young children with anti-NMDAR encephalitis [15].

Table 7  
Comparisons of time to treatment and treatment types among different studies.

	Titualer. <sup>6</sup> (n = 221)	Florence. <sup>5</sup> (n = 32)	Armengue. <sup>4</sup> (n = 20)	Wright. <sup>1</sup> (n = 31)	Anastasia. <sup>7</sup> (n = 36)	Our series (n = 14)
<i>First-line treatment (Median time to first-line treatment)</i>	95% (21 days)	97% (NA)	100% (NA)	100%	100% (19 days)	100% (15 days)
<i>Second-line treatment (Median time from first-line to second-line treatment)</i>	32% (NA)	23% (NA)	35% (NA)	33%	81% (26 days)	57% (54 days)
<i>Type of first-line treatment</i>						
Corticosteroid	84%	NA	100%	100%	86%	100%
Intravenous immunoglobulins	69%	NA	75%	71%	89%	79%
Plasma exchange	33%	NA	5%	29%	39%	21%
<i>Type of second-line treatment</i>						
Rituximab	24%	19%	25%	19%	72%	0%
Cyclophosphamide	16%	16%	10%	19%	14%	57%
<i>Good outcome</i>						
At 12 months	77%	74%*	85%**	NA	83%	62%
At 24 months	87%	NA	NA	NA	83%	81%

NA not available.

\* Only 4.5 months of follow-up.

\*\* 17.5 months of follow-up.

Some previous studies have demonstrated ovarian tumors associated with anti-NMDAR encephalitis in adult patients [8,9]. However, most children in previous research of anti-NMDAR encephalitis did not have underlying tumors [4,5]. Similarly, no patients in our study had an underlying tumor.

In terms of treatment outcome, we observed similar outcomes to those reported in previous international studies [10] (Table 7). Furthermore, we observed better treatment outcomes at 24 months than those at 12 months. These findings suggest that anti-NMDAR encephalitis has a prolonged clinical course, requiring long-term follow-up for at least 24 months. We identified several potential prognostic factors, with altered consciousness and central hypoventilation appearing to predict poor outcome.

Our study is subject to a limitation that should be borne in mind when interpreting the results. Our study recruited a small number of patients as anti-NMDAR encephalitis is a rare disease in children. However, the strength of our study is that it is a multicenter retrospective/prospective cohort study in which we followed patients for 24 months. In additionally, further study should include quality of life and neuropsychological outcome to MRS score. As de Bruijn MAAM et al. demonstrated that many patients have cognitive problem and fatigue resulting in learning problem and impact quality of life [17].

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.braindev.2018.12.009>.

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