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Clinical study

Abnormal level of consciousness predicts outcomes of patients with anti-NMDA encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an acute form of encephalitis with an autoimmune etiology. We aimed to study clinical characteristics and treatment outcomes and assess the predictive factors associated with patient outcome. In this retrospective study, patients who presented with cardinal symptoms of anti-NMDA encephalitis and positive anti-NMDA receptor antibody results in their cerebrospinal fluid were included in the study. Thirty-one patients were identified. The median age of onset was 19 years (IQR 15.0–31.0). Females were predominant (61.8%). The main clinical symptoms were neuropsychiatric symptoms (87.1%) followed by abnormal movement (71%), seizures (51.1%), and autonomic instability (41.9%). Eleven patients (35.5%) exhibited decreased levels of consciousness. Abnormal MRI results were found in only 35.5% of the patients. CSF abnormalities usually involved mild pleocytosis. Only 67.7% of serum samples were positive against the anti-NMDAR antibody, whereas 100% of CSF samples were positive. Tumor-related information was only available for 20 patients. Only one case involved an ovarian teratoma. All patients received first-line therapy (intravenous pulse methylprednisolone and plasmapheresis). Three patients were treated with second-line therapy (IV cyclophosphamide). Twenty patients (64.5%) had favorable outcomes in our cohort (mRS 0–2) after a 1-year follow-up. An abnormal level of consciousness was a factor associated with a nonfavorable outcome (OR 15.65, 95% CI 2.30–106.29, p value <0.01).

1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a form of acute to subacute encephalitis with an autoimmune etiology. The well recognized clinical symptoms of this disease include cognitive dysfunction, behavior change, seizures, speech disorders, movement disorders, alteration of consciousness, autonomic dysfunction, and central hypoventilation [1–3]. Diagnosis is confirmed by the presence of a CSF IgG antibody against the GluN1 subunit of NMDAR [4]. The mainstay of treatment is immunosuppressive therapy including corticosteroid or immunoglobulin with plasma exchange. Patients not responding to first-line therapy are provided with a second-line treatment. Second-line treatments with cyclophosphamide or rituximab have been demonstrated to improve patient outcomes [5]. However, in spite of the established treatment, 17–33% of patients still have poor outcomes [5–8]. The mortality rate ranges from 2.7 to 11.45% [5,7,9,10]. Factors associated with good outcomes include earlier time of treatment [5,11,12], initiation of second-line treatment in patients who did not respond to first-line treatment, no need for intensive care unit admission [5], and an initial-modified ranking score <3 [7]. Moreover, factors affecting nonfavorable outcomes include complications during admission, decreased level of conscious, and central hypoventilation [6,8,13].

In this study, we retrospectively reviewed patients whose diagnosis was anti-NMDAR encephalitis at a tertiary referral neurological center in Thailand. We analyzed the one-year outcome of patients and explored the predictive factors associated with patient outcomes.

2. Methods

We retrospectively reviewed the medical records between January 1st, 2011 and December 31st, 2016 at the Prasat Neurological Institute, which is a tertiary referral neurological center in Thailand. Anti-NMDA encephalitis was diagnosed in patients who presented with cardinal symptoms that were exhibited in previously published studies [1–4] and confirmed by the presence of

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autoantibodies in CSF and/or serum. For antibody testing, serum and CSF screening for autoantibodies were performed by using mouse brains, cerebellums, guts, and kidneys postfixed with 10% formalin. Positive results were confirmed by using cell-based assays in the form of biochips (Euroimmun, Lübeck, Germany). The stained slide and biochips were examined under a fluorescence microscope with Olympus DP72 camera (Olympus Optical Co., Ltd., Tokyo, Japan). The patient's demographics, age of onset, clinical features, duration of admission and treatment course, CSF analysis, brain MRI and EEG findings, presence of tumor, and treatment were recorded. The clinical outcomes in terms of the modified Rankin score (mRS) was evaluated at 12 months in order to ensure adequate time of follow-up. The patients were divided into two groups including patients with a mRS of 0–2, defined as a favorable outcome, and patients with a mRS of 3–6, defined as a nonfavorable outcome. The prognostic factors for nonfavorable outcomes were evaluated in this study. This study was approved by the Medical Ethics Review committee of the Prasat Neurological Institute.

3. Statistical analysis

The frequencies of the symptoms are reported as percentages. The demographic characteristics are reported as medians. The clinical variables were compared between the patients with favorable (mRS 0–2) and nonfavorable (mRS 3–6) outcomes using univariate logistic regression. The variables that were significant in the univariate analysis at $p < 0.1$ were included in a multiple logistic regression model to assess the adjusted association of the variables that appeared predictive. The cut-off for statistical significance was $p < 0.05$.

4. Results

4.1. Patient data, clinical course, investigation, and treatment

Retrospective reviews of the medical records found 31 patients with a diagnosis of anti-NMDA encephalitis. The clinical characteristics are presented in Table 1. The median age of onset was 19 years (IQR 15.0–31.0). Females were predominate (61.8% versus 38.1%). Prodromal symptoms were present in 41.9% of our cohorts. The main clinical symptoms in our cohort were neuropsychiatric symptoms (87.1%) followed by abnormal movement (71%), seizures (51.1%), autonomic instability (41.9%), and speech disorders (16.1%). There were 11 patients (35.5%) that experienced decreased levels of consciousness. Abnormal MRI results were found in only 35.5% of the patients. The majority of abnormal MRI results were T2 signal hyperintensities in the medial temporal area (36.4%). Abnormal EEG results were found in 96.8% of the patients. The most common EEG abnormality was diffuse and slow activity (70.0%). The well recognized EEG pattern in NMDA encephalitis, namely, extreme delta brush [14], was found in 26.7% of patients. CSF pleocytosis was observed only 38.7% of the time, and values were primarily mildly elevated (26.6% with 5–50 cells/dl). No patients in this study had CSF hypoglycorrhachia. Every patient was tested for antibodies against NMDA receptors in both serum and CSF. All of the CSF samples were positive, whereas only 67.7% of serum samples were positive. Investigation for tumors was performed in 20 patients by standard pelvic ultrasound. Only one patient was diagnosed with ovarian teratoma. All patients received first-line therapy (intravenous pulse methylprednisolone and plasmapheresis). The median time from onset to treatment was 24 days (IQR 19.0–34.0 days). Three patients were treated with second-line therapy, which included pulsed high-dose IV cyclophosphamide, due to nonresponse to the first-line therapy. The median time to cyclophosphamide treatment was 77 days (IQR 55.0–205 day). Four patients relapsed even upon receiving immunosuppressive for relapse prevention. Twenty-five patients (80.6%) were admitted to the intensive care unit. The complications along the clinical course were urinary tract infections (16.1%) and pneumonia (32.3%).

Table 1
Clinical characteristics of patients.

Age of onset, median (IQR), years	19.0 (15.0–31.0)
Sex, no. (%)	
Male	12 (38.1)
Female	19 (61.3)
Underlying disease, no. (%)	
medical comorbidity	5 (16.1)
autoimmune disease	2 (6.5)
Prodromal symptoms, no. (%)	13 (41.9)
Clinical symptoms, no. (%)	
cognitive impairment	15 (48.4)
behavioral and neuropsychiatric symptoms	27 (87.1)
speech disorder	5 (16.1)
movement disorder	22 (71.0)
seizures	16 (51.1)
alteration of consciousness	11 (35.5)
autonomic dysfunction	13 (41.9)
EEG findings	
Abnormal, no. (%)	30/31 (96.8)
- Diffuse, slow activity	21/30 (70.0)
- Extreme delta brush	8/30 (26.7)
- Focal slow	5/30 (16.7)
- Electrographic seizure	3/30 (10.0)
MRI findings	
Abnormal, no. (%)	11/29 (35.5)
- Medial temporal T2 hypersignal intensity	4/11 (36.4)
- Multiple extensive cortical subcortical involvement	3/11 (27.3)
- Nonspecific subcortical T2 hypersignal intensity	4/11 (36.4)
CSF	
- Protein >45 mg/dl no. (%)	3/31 (9.7)
- WBC count 5–50 cells/dl no. (%)	7/31 (22.6)
- WBC count >50 cells/dl no. (%)	5/31 (16.1)
- CSF glucose/serum glucose ratio median (IQR)	0.6 (0.6–0.7)
Anti NMDA detection	
Serum: positive	21/31 (67.7)
CSF: positive	31/31 (100.0)
Tumor association (ovarian teratoma) no. (%)	1/20 (5.0)
Relapse no. (%)	4 (12.9)
Treatment	
First-line therapy (intravenous methyl prednisolone and plasma exchange)	31/31 (100.0)
Day from onset, median (IQR)	24 (19–34)
Second-line therapy, no. (%)	
- Cyclophosphamide,	3/31 (9.7)
Day from onset, median (IQR)	77 (55–205)
Relapse prevention, no. (%)	31 (100.0)
ICU Admission, no. (%)	25 (80.6)
Complication, no. (%)	
- Urinary tract infection	5 (16.1)
- Pneumonia	10 (32.3)

4.2. Outcome and predictive factors

Twenty patients (64.5%) had favorable outcomes in our cohort (mRS 0–2) after a 1-year follow-up. The univariate analysis results, in term of patients with nonfavorable outcomes, are shown in Table 2. Altered mental status at the time of presentation was associated with nonfavorable outcomes (OR 15.1, 95% CI 2.48–92.1, p value <0.01). The complications during the clinical course, which were mainly urinary tract infection and pneumonia, were associated with nonfavorable outcomes and showed a nearly statistically

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Table 2
Univariate analysis of potential predictive factors for patients with nonfavorable outcomes.

Variable	P value	Odds ratios (95% CI)
Age	0.840	0.99 (0.93–1.06)
Age ≤15 years (vs >15 years)	0.325	0.44 (0.08–2.26)
Sex	0.337	0.46 (0.09–2.25)
Clinical symptoms		
cognitive impairment	0.981	1.02 (0.23–4.46)
neuropsychiatric symptoms	0.441	2.50 (0.24–25.68)
speech disorder	0.441	0.40 (0.04–4.11)
movement disorder	0.052	4.95 (0.98–24.87)
seizures	0.612	0.68 (0.16–2.99)
alteration of consciousness	<0.001*	15.10 (2.48–92.10)
autonomic dysfunction	0.107	3.60 (0.75–17.13)
MRI abnormality	0.161	3.60 (0.60–21.61)
CSF abnormality		
- Protein >45 mg/dl	0.264	0.24 (0.02–2.96)
- WBC >50 cells/dl	0.818	1.26 (0.18–8.97)
ICU admission	0.303	3.33 (0.34–32.96)
Complication (pneumonia and urinary tract infection)	0.10	3.60 (0.76–17.13)
Time to treatment	0.497	1.01 (0.98–1.04)
Early treatment ≤15 days (vs. >15 days)	0.902	1.12 (0.17–7.40)
Relapse disease	0.110	7.13 (0.64–79.27)

* Indicated significant difference with P < 0.05.

significant relation (OR 3.60, 95% CI 0.76–17.13, p value = 0.10). Three patients who received second-line therapy had nonfavorable outcomes in the study. Other factors, such as age of onset, time to treatment, sex, tumor association, median time to treatment, relapse disease, ICU admission, CSF profile, MRI, and EEG findings, were not significant predictive factors for clinical outcomes. In multivariate analysis, altered mental status was the only factor associated with nonfavorable outcomes (OR 12.02, 95% CI 1.66–86.71, p value = 0.014).

5. Discussion

In this study, we described 31 patients diagnosed with anti-NMDA encephalitis confirmed by cardinal symptoms that were based on previously published studies and the detection of a specific antibody to the NMDA receptor in CSF. The median age of onset was 19 years, and patients were predominantly female. Patients usually presented with neuropsychiatric symptoms, cognitive impairment, seizures, and abnormal movement. MRI abnormalities were found for only 35.5% of patients in the present study. These data correspond with a recent systematic review indicating that less than half of MRI results for patients with anti-NMDA encephalitis show abnormal findings [15]. EEG abnormalities are common in patients with anti-NMDA encephalitis [4,16]. Our data showed that 96.8% of findings were abnormal. The majority of EEG abnormalities were diffuse and slow activity, which are nonspecific. These conditions can be found in association with any cause of encephalopathy. There is a specific EEG pattern in patients with anti-NMDA encephalitis called extreme delta brush, which was found in 26.7% of our patients. This positivity rate was small compared to the entire cohort and was similar with that of a previously published study [14], which showed a rate of 30.4%. Therefore, the diagnosis relied on clinical symptoms and positive anti-NMDA receptor antibody results in CSF. The positive rate of anti-NMDA antibody detection was 100% in CSF, but it was only 66.7% in CSF. This indicated higher sensitivity of CSF compare to serum testing. In the present study, 64.5% of patients had favorable outcomes (mRS 0–2) at the one-year follow up. The predictive factor of nonfavorable outcomes was patients who experienced decreased levels of consciousness during the clinical course. This result is similar to findings from Chinese and Korean cohorts [6,8]. In the large cohort study by Titulaer et al. [5] one of the factors associated with good outcomes was no admission to the intensive care unit. This might imply that the patients who need ICU admission experienced decreased levels of consciousness. A decreased level of consciousness in patients with anti-NMDA encephalitis might indicate the severity of the disease compared to patents who had consciousness levels that were preserved. Other possible explanations for poor outcomes in patients with decreased levels of conscious might be the delayed diagnosis leading to progression of the disease and delayed treatment. However, compared to the entire cohort, patients with altered mental status had similar times from onset and treatment (24 days, IQR 19–30 vs 24 days, IQR 19–34). These results might support that anti-NMDA encephalitis should be classified according to disease severity, because prognoses were different with requirements for early detection and aggressive treatment to improve patient outcomes. Complication during admission, such as pneumonia and respiratory failure, also effected patient outcome and mortality [8,10]. In our data, a complication during admission might have a confounding effect on patient outcome. Patient who experience decreased levels of consciousness might require prolonged intubation leading to the more complications, such as hospital-acquired pneumonia. Other factors, such as age of onset, time to treatment, sex, tumor association, median time to treatment, disease relapse, ICU admission, CSF profile, and MRI and EEG findings, were not related to the clinical outcomes in our study. Moreover, early initiation of immunotherapy showed benefit for patients with anti-NMDA encephalitis [5,11,12]. In our study, early initiation of treatment did not demonstrate benefits to patient outcomes, which may be explained by the average median time to treatment in our study, which was relatively long. Patients were usually referred to our center and typically took almost a month before receiving the correct diagnosis and starting treatment, which might lead to the loss of the benefit of early immunotherapy. The benefit of second-line therapy in patients who did not respond to first-line therapy was demonstrated in patients with NMDA encephalitis in a previous study [5], but this approach did not show benefits in our study. All three patients in the second-line therapy group were associated with poor outcomes even at the follow-up time of 12 months. This may be due to a relatively long interval to treatment with second-line therapy, with a median of 77 days (IQR 55.0–205.0). There was only one ovarian teratoma detected from 20 patients (5%), for which a standard pelvic ultrasound was performed. There was a lower percentage of ovarian teratomas compared to a previous report that showed a rate of 38% [5]. This can be explained by two different perspectives. The standard pelvic ultrasound has a low sensitivity to detect ovarian teratomas, especially for small tumors. Another approach, such as computed tomography pelvic imaging or transvaginal ultrasound, might be suitable to investigate patients with anti-NMDA encephalitis. Another explanation for the lower percentage of tumors associated with our cohort is because the true prevalence of tumors associated with anti-NMDA receptor encephalitis is possibly lower in Asian countries compared to that in the Western population. These data are supported by the prevalence of tumors of patients with anti-NMDA encephalitis in the Korean and Chinese population which is relatively low compared to that in Western countries: 22% and 8% respectively [6,8]. These data suggested ethnicity-specific factors in difference ethnic groups. There is also evidence from previous studies indicating that black women are more likely to have an underlying ovarian teratoma than other ethnic groups [4].

The limitation of our study is the retrospective design, as the study was based in a single center. The clinical evaluation and

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responses to therapy were based on physician reports documented in the medical records.

Conflict of interest

The authors declare no financial or other conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2018.11.033.

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