Journal of Neuroimmunology 324 (2018) 119–125

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Heterogenous treatment for anti-NMDAR encephalitis in children leads to different outcomes 6–12 months after diagnosis

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ARTICLE INFO

Keywords:
Anti-*N*-methyl-D-aspartate receptor encephalitis
IVIG
Outcome
Children

ABSTRACT

Recommended first line treatment in anti-NMDAR encephalitis includes steroids, IVIG, or plasma exchange. However, IVIG is non-reimbursable through Thailand's Universal Health Coverage. This study investigated outcomes from different treatments for anti-NMDAR encephalitis. Nineteen children in three treatments group: steroid alone, IVIG alone, and IVIG and steroid were reviewed. IVIG was administered to 13 (68%) and 6 (32%) only received steroids. Those receiving IVIG treatment with or without steroids had greater improvement in mRS at 6 ($p = 0.04$) and 12 months ($p = 0.03$). Such findings suggest the benefits of IVIG treatment for this condition despite the higher immediate cost.

1. Introduction

Anti-N-Methyl-D-Aspartate receptor (NMDAR) encephalitis has become an increasingly recognized autoimmune encephalitis over the last decade, and is now the second most frequent autoimmune central neurological disease in children.(Dalmau et al., 2007; Granerod et al., 2010; Gable et al., 2012) The disorder was first described in young women who presented with acute psychosis associated with an ovarian teratoma. Subsequent cases reported in adults and children occurred without underlying tumors.(Vitaliani et al., 2005; Titulaer et al., 2013; Florance et al., 2009) Clinically, anti-NMDAR encephalitis in children shares a similar constellation of symptoms observed in adults, but tend to have more neurologic features such as seizures or dyskinesias, rather than psychiatric ones and are less often associated with tumors. (Armangue et al., 2013)

The current first line treatment recommendations, based on the proposed disease mechanism of surface antibodies, are high dose corticosteroids, intravenous immunoglobulin (IVIG), or plasma exchange (PE).(Titulaer et al., 2013; Dalmau et al., 2011) Tumors should be removed if present. When treated with immunotherapy, anti-NMDAR encephalitis patients tend to have better outcomes than those diagnosed with viral encephalitis.(Granerod et al., 2010; Titulaer et al., 2013; Dalmau et al., 2011; Irani et al., 2010; Sartori et al., 2015) Yet, despite published treatment recommendations and success, guidelines regulating IVIG use vary in different countries.(Nosadini et al., 2016) Such variation is likely attributable to the cost of IVIG; countries such as Thailand cannot justify using this expensive treatment in the absence of more concrete evidence from randomized control trials. Therefore, in Thailand, IVIG is not reimbursed with the Universal Health Coverage scheme (UHC). The other treatment option, PE, is challenging in children due to technical concerns. These limitations have led to treatment heterogeneity based on disease severity, socioeconomic status, and treating physician practice rather than standardized evidence-based practice.

To understand the differential disease burden caused by the inconsistent treatment modality for this condition, our study aimed to define the clinical features, treatment course, efficacy, and clinical outcomes among anti-NMDAR encephalitis patients.

2. Patients and methods

This observational cohort study was conducted at Queen Sirikit National Institute of Child Health, the largest government children hospital in Thailand. Children aged 1 months - 18 years diagnosed with anti-NMDAR encephalitis by presence of NMDAR antibodies in serum and/or CSF between January 1, 2011, and June 30, 2017, were

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https://doi.org/10.1016/j.jneuroim.2018.09.007
Received 5 August 2018; Received in revised form 9 September 2018; Accepted 17 September 2018

recruited in this study. This cohort was divided into two periods: children diagnosed before January 1, 2016 that were retrospectively studied and those diagnosed after Jan 1, 2016 that were prospectively evaluated. All participants and families provided informed consent. This study was approved by the Research Ethics Review Committee of Queen Sirikit National Institute of Child Health.

Demographic, clinical features, treatment, and clinical outcomes were collected from the medical record. Clinical manifestations were classified into eight groups: psychiatric/behavioral, seizures, movement disorder, speech impairment, sleep disturbance, reduction in level of consciousness, autonomic dysfunction, and central hypoventilation. Investigation results of neuroimaging, electroencephalogram (EEG), and CSF examinations were recorded. CSF abnormalities were defined as any of the following: pressure > 180 mmH_2O, total white blood cell > 5 cells/μl, or total protein > 0.50 g/l.(Wang et al., 2015) Acute immunotherapy management was based on attending pediatric neurologist's decision, the severity of disease, health insurances, and family socioeconomic status. The acute immunotherapy groups were divided into 1) steroid alone, 2) IVIG alone, and 3) IVIG combined with a steroid. Eligible subjects were classified into the following health insurance schemes: 1) Universal Health Coverage (UHC), 2) Civil Servant Medical Benefit Scheme (CSMBS), and 3) Self-pay.(Tangcharoensathien et al., 2018) IVIG treatment for anti-NMDAR encephalitis was covered by CSMBS but not through UHC during this period. Tumor screening results and removal were recorded. We assessed neurological status with a modified Rankin scale (mRS) at post-discharge follow-up (1, 2, 4, 6, 8, 10, and 12 months).(Palisano et al., 1997; Van Swieten et al., 1988) Modified Rankin scores in this study were assessed at six months. At this time point, a good outcome was defined as an mRS of 0–2 without relapse, and a poor outcome was taken as an mRS of 3–6 or relapse. We defined relapse as the new onset or worsening symptoms after improvement or stabilization.

The NMDAR antibodies test used in this study became available at Prasat Neurological Institute, Bangkok, Thailand starting in 2010. We sent all the serum and cerebrospinal fluid (CSF) for this study to the institute for analysis and comparison with healthy controls. Tissue immunohistochemistry assays were conducted using mouse brain composite substrate (hippocampus, forebrain, and cerebellum). Fluorescent-dye conjugated goat anti-human IgG were used to identify NMDAR antibodies; stain patterns were assessed as positive when noticed at the granular layer of the cerebellum and the hippocampus. Cell-based assays (CBAs) using human embryonic kidney 293 (HEK293) cells transfected with the NR1 subunit of the NMDA receptor were performed. These fixed CBAs were analyzed under microscope. A staining pattern on the cell surface for at least five fields per well and distribution of stained cells were considered positive. If there was a high background that may interfere the interpretation, the sample was spun with centrifuge (14,000 rpm) and the supernatant was retested. Both assays were compared with a positive and negative control.

Descriptive data summaries were generated using frequency distributions (number and percentage). Continuous data are reported as means with standard deviations or medians with interquartile range (IQR). Comparisons of categorical data were conducted using Fisher's exact tests. Continuous data were analyzed using Kruskal-Wallis test. The clinical severity documented by mRS score at each time point during follow-up were analyzed with repeated measures to determine the changes in mRS score over time. A multivariate regression model including potential modifiers of the relationship between treatment and outcome was performed to determine what factors if any, remained predictive for good outcome. Early treatment was defined as initial symptom to treatment < 40 days.(Irani et al., 2010) All statistical analyses were performed on IBM SPSS version 18.0. Statistical significances were determined as $p < 0.05$.

3. Results

Nineteen children were diagnosed with anti-NMDAR encephalitis over the 6.5-year period. The median age of the patients was 7 years 4 month (IQR 5.0, 11.1). Eleven patients (58%) were female. The ratio of female to male was similar within each age group, with eight (57%) in fourteen of the patients < 12 years and three (60%) in five ≥12 years were female. Fourteen patients were covered under UHC (74%), one through CSMBS (5%), and the remaining four were self-pay (21%). Details of demographic information, clinical characteristics, investigations, treatments are summarized in Table 1.

The initial presenting symptom was seizures in ten (53%), psychiatric problems or behavioral changes in eight (42%), and movement disorder in one (5%). Thereafter, nearly all children (90%) developed psychiatric symptoms or abnormal movements, 84% seizures, 68% autonomic instability (included tachycardia, bradycardia,

Table 1
Clinical features, investigations, treatment and outcomes of children with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis.

Case	Age, yr; Sex	Initial symptom	Time to treatment (days)	CSF pleocytosis	NMDAR ab, CSF/serum	mRS max	Health insurance	Treatment	Tumor	Relapse	Outcome
1	6.6; F	Psy	30	+	+/+	5	UHC	IVIG	−	−	Good
2	7.8; M	Sz	60	−	NA/+	2	Self-pay	IVIG	NA	−	Good
3	12.9; F	Sz	36	−	+/+	5	UHC	Steroid	−	+	Good
4	8.0; M	Sz	7	+	+/+	5	UHC	IVIG, Steroid	−	−	Good
5	14.0; M	Sz	12	−	+/+	4	UHC	IVIG, Steroid	NA	−	Good
6	7.3; F	Psy	60	−	+/+	3	UHC	IVIG	−	−	Good
7	5.8; M	Psy	20	−	+/+	4	UHC	IVIG	NA	−	NA
8	2.7; F	Sz	21	+	+/+	4	Self-pay	IVIG, Steroid	−	−	Good
9	9.7; F	Psy	50	−	+/+	2	UHC	Steroid	−		Good
10	2.2; M	Sz	51	−	+/+	5	Self-pay	IVIG, Steroid	NA	−	Good
11	4.5; F	Sz	16	+	+/+	5	UHC	Steroid	−	−	Poor
12	12.6; F	Psy	5	+	+/+	5	UHC	IVIG, Steroid	+	−	Good
13	4.5; F	Sz	31	−	+/+	2	CSMBS	IVIG	−	−	Good
14	0.8; M	Sz	42	+	−/+	4	UHC	Steroid	NA	−	Good
15	8.8; M	MD	205	+	−/+	4	Self-pay	IVIG, Steroid	−	+	Poor
16	7.3; F	Psy	9	+	+/+	3	UHC	Steroid	−	−	Good
17	6.5; F	Psy	17	−	+/+	4	UHC	IVIG, Steroid	−	+	Poor
18	14.4; M	Sz	11	+	+/+	2	UHC	Steroid	NA	−	NA
19	12.7; F	Psy	8	+	NA/+	4	UHC	IVIG, Steroid	+	−	Good

Good outcome = mRS 0–2 without relapse at six months visit; Poor outcome = mRS > 2 at six months visit or relapse within six months after diagnosis.
+, positive; −, negative; ab = antibodies; CSMBS = Civil Servant Medical Benefit Scheme; CSF = cerebrospinal fluid; F = female; IVIG = intravenous immunoglobulin; M = male; MD = movement disorder; mRS = modified Rankin Scale; NA = not applicable; Psy = psychiatric problems or behavioral changes; Sz = seizures; UHC = Universal Health Coverage Scheme; yr = years.

Table 2
Baseline clinical characteristics among the three treatment groups of anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis patients.

Characteristic	Steroid alone* N = 6	IVIG alone *N* = 5	IVIG and steroid *N* = 8	P
Median age, IQR (year)	8.5 (3.5, 13.3)	6.6 (5.1, 7.5)	8.4 (3.6, 12.6)	0.62¶
Median interval between onset and diagnosis, IQR (days)	26 (10.5, 44)	31 (25, 60)	14.5 (7.3, 43.5)	0.26¶
Median length of hospitalization, IQR (days)	24.5 (9.3, 57.5)	10 (5.5, 32.5)	15 (10.5, 28.5)	0.61¶
Median maximum mRS before immunotherapy, IQR	3.5 (2, 5)	3 (2, 4.5)	4 (4, 5)	0.22¶
Female	4 (66%)	3 (60%)	4 (50%)	0.82§
Abnormal MRI†	3 (60%)	1 (25%)	2 (28%)	0.45§
Abnormal CSF	4 (67%)	1 (20%)	6 (75%)	0.13§
Abnormal EEG	5 (83%)	3 (60%)	7 (88%)	0.47§
Intubation	1 (17%)	0	3 (38%)	0.34§
ICU admission	1 (17%)	0	2 (25%)	0.56§
Tumor	0	0	2 (25%)	0.28§
UHC insurance	6 (100%)	3 (60%)	5 (63%)	0.21§

CSF = cerebrospinal fluid; EEG = electroencephalography; ICU = intensive care unit; IVIG = intravenous immunoglobulin; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; UHC = universal health coverage.

¶ Kruskal Wallis test.

§ Fisher's exact test.

* One patient in the steroid alone group was treated with azathioprine as maintenance treatment after diagnosis and receiving acute immunotherapy.

† MRI information was available was total available in 16 patients; 4 in IVIG alone, 5 in steroid alone, and 7 in IVIG and steroid group.

hypertension, and hyperthermia), 47% impaired speech, 32% decreased level of consciousness, 11% central hypoventilation, 11% sleep disturbance, and other symptoms including hemiparesis and ataxia in 10%. Most of the patients (84%) had three or more groups of symptoms, three (16%) developed two symptoms, and none had only one symptom. The median time from presentation with initial symptoms until treatment for the 14 patients (74%) studied retrospectively was 30.5 days (IQR 15, 50.5). This was almost three times longer than the five patients (26%) studied prospectively, for whom the median time was 11 days (IQR 9, 17) ($p = 0.44$). The median length of hospitalization was 15 days (IQR 10, 31.5). Four patients (21%) required intubation and three (18%) were admitted in the intensive care unit (ICU). Of these three, the median days in ICU stay was 15 (IQR 12, 14).

NMDAR antibodies were detected in the CSF in 19 (100%) of patients, and in the serum in 15 of 17 (88%) patients. The CSF examination showed elevated pressure (> 180 mm H_2O) in eight of 10 (80%) patients (median pressure 25 cmH_2O; IQR 20, 28), lymphocytic pleocytosis in 10 of 19 (53%) (median 19 cells/μL; IQR 1, 25), and elevated protein concentration in three of 18 (17%) (median 38 mg/dl; IQR 21.1, 31.6). Of eight patients who had elevated CSF pressure, none had clinical features of raised intracranial pressure. The EEG recording during the maximal mRS in each patient was abnormal in 15 (79%) patients: slow activity in 12 (80%), focal epileptiform discharges in six (40%), and extreme delta brush pattern in two (13%). Six (38%) of the 16 patients that underwent brain MRI revealed abnormalities: three had abnormal hyperintensities in unilateral cortical regions, one had abnormal hyperintensities in bilateral basal ganglia and temporal lobes, one with diffuse leptomeningeal enhancement, and one had increased patchy confluent extension of lesions in subcortical white matter (compared to the previous imaging when was ADEM diagnosed).

Eight patients (42%) initially received a combination of high dose intravenous methylprednisolone (30 mg/kg/day for 3–5 days) and IVIG (total dose 2 g/kg/course), six (32%) were treated only with steroids (three (50%) with high dose intravenous methylprednisolone and three (50%) with intravenous dexamethasone), five (26%) received IVIG alone. IVIG was administered less in the UHC group when compared to patients in the non-UHC group: only eight (57%) of 14 patients with UHC were treated with IVIG while all five (100%) in the non-UHC group were treated with IVIG ($p = 0.13$). The median of maximum mRS before starting treatment was 4 (IQR 4, 5) in the IVIG and steroid group, 3.5 (IQR 2, 5) in steroid alone group, and 3 (IQR 2, 4.5) in the IVIG alone group. There was no statistically significant difference in initial mRS between groups ($p = 0.22$). The median length of hospitalization was 24.5 days (IQR 9.3, 57.5) in the steroid alone group, 15 days (IQR 10.5, 28.5) in IVIG and steroid group, and 10 days (IQR 5.5, 32.5) in the IVIG alone group. The difference in length of hospital stay was not significant between treatment groups ($p = 0.61$). The other clinical features among different treatment groups also did not differ. (Table 2) For maintenance treatment after receiving acute immunotherapy, 16 patients (84%) were administered with oral prednisolone (0.5–2 mg/kg/day), one patient (5%) was treated with prednisolone and azathioprine, and two (11%) did not receive any maintenance therapy. Of these two, one was in the steroid alone group and one was in the IVIG alone group. The median duration of oral prednisolone was 3.5 months (IQR 1.8, 7.5). Three patients (16%) received chronic immunotherapy with prednisolone for > 6 months. Azathioprine (1–3 mg/kg/day) was administered in three cases, two were in the IVIG and steroid treatment group, and one was in the steroid alone group. Two patients in the IVIG and steroid group were administered with azathioprine after relapse and the other in the steroid alone group received azathioprine after the diagnosis and acute immunotherapy. Tumors were found and removed in two of 13 (15%) screened. Both patients that required tumor removal were in the IVIG and steroid treatment group and ≥ 12 years old: one had an immature teratoma that was found and removed during the admission and treatment of the condition and one was a fully recovered patient with a mature teratoma found in a fully recovered patient in the fifth tumor surveillance two years after diagnosis.

The outcome was assessable in 17 (89%) and 15 (79%) patients at six and 12 months, respectively. The median duration of follow-up was 30 months (IQR 19, 42). Of the 17 children assessed at six months, there were no deaths, 14 (82%) had good outcome (mRS 0–2) and three (18%) had poor outcome. Most of the patients improved gradually over time after treatment (Fig. 1). The patients who received IVIG, regardless of whether steroids were also administered, showed a decreasing mRS trend over time compared to those who received steroids alone at six months ($p = 0.13$) and 12 months ($p = 0.12$) (Fig. 2A). We further subcategorized the treatment groups into those received IVIG ($n = 13$) and those that did not ($n = 6$). The median maximum mRS in the IVIG group was 4 (IQR 3.5, 5) and in the steroid alone group was 3 (IQR 2, 5). As seen in prior analysis between the original three treatment

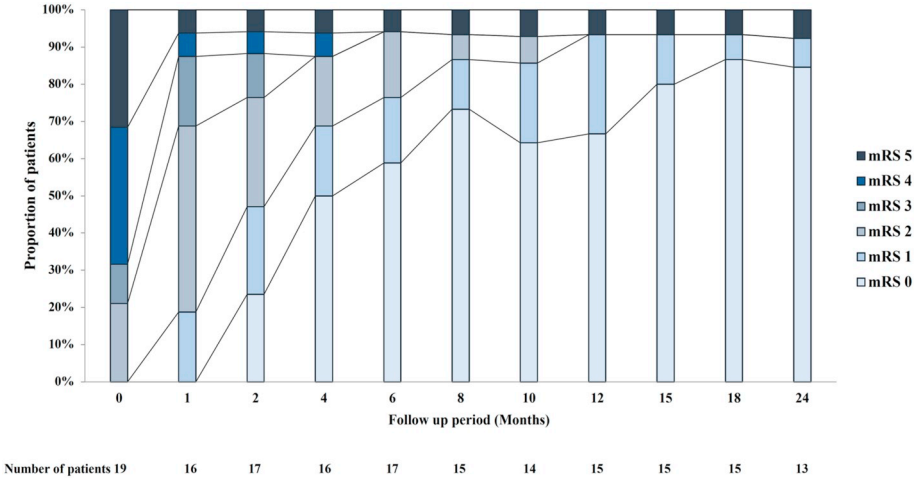

Fig. 1. Clinical outcome in all children with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis.

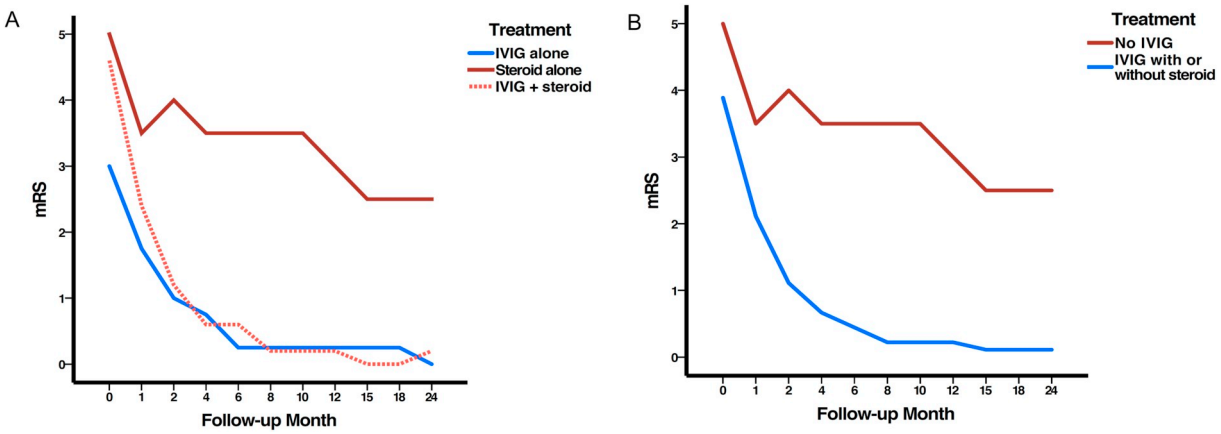

Fig. 2. Clinical outcomes assessment in according to treatments at 6 months (n = 17) and 12 months (n = 15); A: the trend of mRS reduction according to three types of treatments at 6 months (p = 0.13) and 12 months (p = 0.12), B: mRS reduction according to received IVIG or not at 6 months (p = 0.04) and 12 months (p = 0.03) mRS = modified Rankin Scale.

groups, clinical characteristics among two subgroups did not differ. Patients who received IVIG had decreased in mRS at both six (p = 0.04) and 12 month follow-up period (p = 0.03) compared to the patients not receiving IVIG (Fig. 2B). The length of hospitalization in patients treated with IVIG with or without steroid was 15 days (IQR 9, 28) that was shorter compared to those who received steroid alone was 24.5 days (IQR 9.3, 57.5). However, the difference was not significant (p = 0.15).

We conducted univariate and multivariate analysis to determine what factors were independently predictive of the outcome. Three study participants were excluded from this analysis: two patients without 6 month follow up data and one patient who received azathioprine early after diagnosis. The patient receiving azathioprine early was excluded because the early azathioprine treatment may be a modifying factor. We analyzed intubation that reflected directly on the patient severity instead of ICU admission because the ICU admission depended on the ICU bed availability. Age, sex, duration from initial symptom to treatment, initial maximum mRS before treatment, intubation, and health insurance were not significantly related with the outcomes. (Table 3).

Table 3
Clinical factors associated with outcome in anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis patients.

Factor	Good outcome*N = 13	Poor outcome‡N = 3	Univariate	Multivariate	
			P	P	OR (95% CI)
Female	8 (62%)	2 (67%)	1.0	0.90	1.21 (0.07–38.77)
Age > 12 years	9 (69%)	0	0.53	–	–
Early treatment (< 40 days)	8 (62%)	2 (67%)	1.0	0.96	0.91 (0.03–26.46)
Initial maximum mRS ≥ 4	9 (69%)	3 (100%)	0.53	–	–
Intubation	3 (23%)	1 (33%)	1.0	0.74	1.69 (0.74–38.76)
UHC insurance	9 (69%)	2 (67%)	1.0	–	–

mRS = modified Rankin Scale; UHC = universal health coverage.
* Good outcome = mRS 0–2 without relapse at six months visit.
‡ Poor outcome = mRS 3–6 at six months visit or relapse within six months after diagnosis.

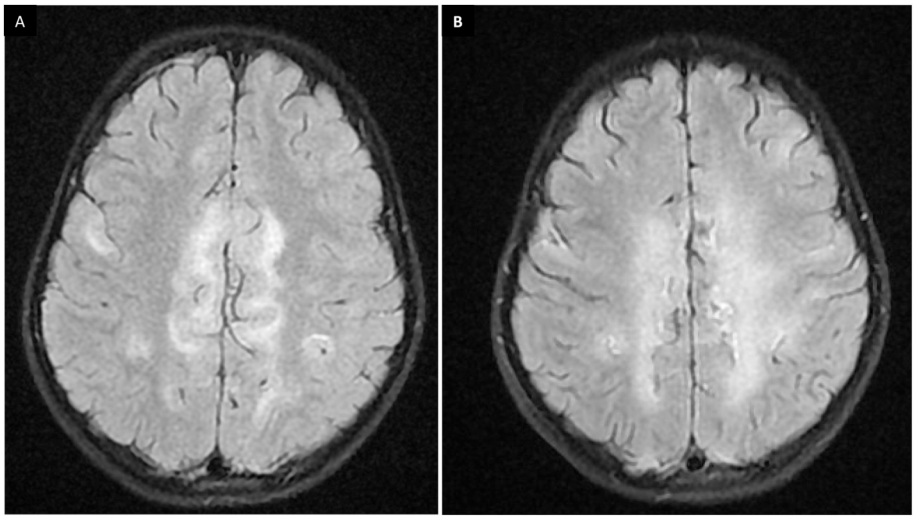

Fig. 3. Axial brain magnetic resonance imaging (MRI) in patient 11 (see Table 1) with acute disseminated encephalomyelitis (ADEM) 4 weeks prior diagnosis of anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis. (A) There are areas of increased fluid-attenuated inversion recovery (FLAIR) signal involving bilateral parasagittal frontal subcortical white matter when diagnosed with ADEM. (B) Image shows increased extension of patchy confluent lesions. NMDAR antibodies were also identified in serum and cerebrospinal fluid.

Poor outcomes were identified in three patients: one with severe neurological deficits and two with relapse during the first six-month period (one patient at two months and the other at five months). The worst outcome in this study was four-year-old girl (case#11 in Table 1) with history of ADEM 4 weeks prior to diagnosis with anti-NMDAR encephalitis. ADEM was diagnosed based on clinical features with weakness and encephalopathy combined with MRI findings revealing multiple asymmetric hyperintensity in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (Fig. 3A). She received treatment with five days of high dose methylprednisolone (30 mg/kg/day) and showed dramatic improvement: she was speaking normally and returned to her baseline prior to admission. She was subsequently discharged. However, four weeks later she developed focal aware seizures. MRI was repeated and showed increased patchy confluent extension of lesions in subcortical white matter in T2-weighted and FLAIR sequences (Fig. 3B). Seizures were refractory to control with antiepileptic drugs and orofacial dyskinesia was noticed at that time. Thus, antibodies to NMDA receptor was tested and proved positive in serum and CSF; she was then restarted with new course of methylprednisolone. She was unable to walk and required nursing care at six and 12 months even though seizures were controlled.

In addition to the two relapses occurring in the first six-month period, one additional patient relapsed at 30 months, making a total of three patients (18%). Two were in the IVIG and steroid treatment group and the other was in the steroid alone group. One had a single episode and two patients had two episodes. The first relapse occurring at two, five and 30 months after diagnosis had milder symptoms compared to those they presented with at the time of initial diagnosis. All relapse episodes were treated with acute immunotherapy, two were received with high dose intravenous methylprednisolone, and the other was treated with combination of IVIG and steroid. Two patients received azathioprine as a maintenance treatment after administration with acute immunotherapy and the other had no maintenance therapy. None of these patients had a tumor at presentation or at relapse. No factors analyzed in this study were associated with relapse.

4. Discussion

This study provides the clinical outcomes of anti-NMDAR encephalitis in children who, as a consequence of the limitation of health insurances, received a variety of different treatments. The current recommended treatment of high dose corticosteroids combined with IVIG or PE is tentative based on Class IV evidence.(Titulaer et al., 2013; Dalmau et al., 2011; Irani et al., 2010; Bartolini, 2016; Gronseth et al., 2011) A recent study showed treatment differences worldwide due to the lack of sufficient evidence to create consensus on the best treatment for this disorder (Bartolini and Muscal, 2017). IVIG treatment is used widely in children with various immune-mediated neurological conditions without strong evidence (Nosadini et al., 2016). Of those immune-mediated neurological disorders, anti-NMDAR encephalitis patients tended to benefit most from IVIG treatment, with 87.5% demonstrating a reduction in mRS to normal levels (0–2). This is especially profound considering IVIG treatment cost the least among anti-NMDAR encephalitis patients when compared to other neuroimmunological conditions (Nosadini et al., 2016).

As noted from the previous studies, clinically marked improvement or full recovery ranged from 74% to 85%, similar to our findings that 82% of patients had good six month outcomes.(Gable et al., 2012; Vitaliani et al., 2005; Armangue et al., 2013; Dalmau et al., 2011; Sartori et al., 2015) Further, in our study IVIG treatment alone or with steroid showed greater improvement in mRS over time when compared with steroid treatment alone. This finding is supported by the previous studies that showed better outcomes among both adults and children when corticosteroids were combined with at least one other immunotherapy rather than given alone.(Irani et al., 2010; DeSena et al., 2015) This combined treatment may work better than any treatment alone because anti-NMDAR encephalitis is postulated to be caused when NMDAR antibodies bind to neuronal surface proteins; IVIG treatment can prevent this binding by removing circulating NMDAR antibodies, and steroids provide additional support by attenuating antibody production (Dalmau and Graus, 2018). To determine whether or not the combined treatment is more effective than IVIG alone, a larger sample of each treatment group is necessary.

Some reported predictors for good outcome not found in this study may include faster initiation of treatment, earlier tumor removal, lack of ICU admission, and the use of second-line immunotherapy in patients who did not respond well to the first line treatment.(Titulaer et al., 2013; Irani et al., 2010) Second-line treatment options including rituximab, cyclophosphamide, or combination have shown promising treatment effect.(Titulaer et al., 2013; Dalmau et al., 2011) Rituximab administration resulted in general improvement in mRS score, but the effect was greater in patients that received rituximab earlier in the disease course.(Dale et al., 2014) Cyclophosphamide monthly alone or combination with rituximab is the alternative second-line treatment and has beneficial effect in children who did not respond with the first line treatment.(Armangue et al., 2013; Zekeridou et al., 2015)

The most common presenting clinical symptom in our study was seizures, in line with prior studies suggesting that children present more commonly with neurological symptoms than the psychiatric ones typically seen in adults.(Gable et al., 2012; Armangue et al., 2013) Almost

all children subsequently developed behavioral changes or psychiatric problems, abnormal movements, and seizures. These are consistent features during the course of illness regardless of initial presentation. Nearly all of the patients in this study had ≥3 symptoms, and the remaining patients had at least two. These findings are supported by those of a large cohort study suggesting that this disorder is a syndrome consisting of a specific group of symptoms and therefore clinicians should be cautious when assigning this diagnosis to children with a single isolated symptom (Titulaer et al., 2013). Other clinical manifestations were also similar to previous pediatric studies (Florance et al., 2009; Armangue et al., 2013). A slight female preponderance was found in our study, but the percentages were not high as in prior investigations. This observation may be explained by the lower median age of our cohort as three quarters were younger than 12 years.

The youngest child in this study was nine months. While data is limited on infants with anti-NMDAR encephalitis, this study and others have shown that even though infants do not have the same obvious clinical symptoms as older children or adults, they still may suffer from anti-NMDAR encephalitis. These findings should be used to promote the physician awareness and help with diagnosis in younger populations (Goenka et al., 2017).

The frequency of CSF pleocytosis, half of the patients in our study, is on the lower side of the large range determined in previous research (Dalmau et al., 2007; Titulaer et al., 2013;Armangue et al., 2013; Dalmau et al., 2011; Wang et al., 2017). MRI abnormalities were present in a third of this cohort in line with the prior case series (Gable et al., 2012; Titulaer et al., 2013; Armangue et al., 2013). Similar to previous studies, EEG abnormalities were detected in 80% of patients, with diffuse slow activity being the most common finding.(Dalmau et al., 2007; Gable et al., 2012; Titulaer et al., 2013;Armangue et al., 2013; Dalmau et al., 2011) The specific pattern, extreme delta brushes, was found in 13% in our study. The number is lower than those generated in adult cohorts but higher than past studies in similar pediatric populations (Armangue et al., 2013; Schmitt et al., 2012; Nagappa et al., 2016). Overall, there is demonstrated variability of ancillary tests abnormalities likely owing to the early or late stages when a child gets the diagnosis of this condition (Irani et al., 2010).

The worst outcome in this study was the patient who developed anti-NMDAR encephalitis after diagnosis of ADEM, an unsurprising finding given that a previous study reported that patients with overlapping demyelinating syndromes and anti-NMDAR encephalitis required more intensive therapy and experienced more residual deficits compared to typical anti-NMDAR encephalitis.(Titulaer et al., 2014) Testing for aquaporin-4 (AQP4) antibodies and myelin oligodendrocyte glycoprotein (MOG) antibodies in the patients with anti-NMDAR encephalitis who have demyelinating features is suggested to recognize the coexistence of two active immune mechanisms.(Titulaer et al., 2014) However, we are unable to confirm that this was true in the case presented in this study because the AQP4 antibody was not tested and the MOG antibody test was not available at that time. Archive serum was not available to run the tests at this time.

The relapse rate in our cohort was one fifth, in line with previous studies both in Thailand and other countries.(Gable et al., 2012; Titulaer et al., 2013; Armangue et al., 2013; Chanvanichtrakool et al., 2017) The frequency of ovarian tumors in our study found only in patients ≥12 years old, was 10%, consistent with prior reports. (Titulaer et al., 2013; Armangue et al., 2013; Irani et al., 2010) In the previous Thai study, however, no tumors were found. The low rate of tumors raised questions about how often and for how long we should perform tumor surveillance in children diagnosed with anti-NMDAR encephalitis; this question is particularly important in cohorts < 12 years old, where tumors are even less common.

Our study has some potential limitations. First, this was an observational study and had no uniform diagnostic and treatment approach; NMDR antibodies test were not routinely performed in all children with some form of encephalitis. Additionally, though the study recruited participants both retrospectively and prospectively for combined analysis, there may be some heterogeneity between groups. Most notably, treatment initiation for those in the retrospective group was much later than participants in the prospective one. Second, mRS is a crude marker to assess the outcome and examiners were unblinded in mRS scoring. Third, this was a single site study of a low-resource population, and as such may not be generalizable. Fourth, our small sample size may not have enough power to find predictors with smaller effect sizes. This may explain why our study, when compared to others, did not demonstrate many more factors significantly associated with the good outcome.

In conclusion, anti-NMDAR encephalitis is a distinct clinical syndrome and physician awareness regarding the good outcomes with immunotherapy treatment needs to be promoted. The patients who received IVIG treatment with or without steroids had improved outcome at 6 and 12 months compared to the patients who received steroid treatment alone and we postulate likely lead to reduce long term costs. These observational findings suggest that IVIG should be considered and offered to all children with anti-NMDAR encephalitis despite limited resources and encourage more rigorous research to confirm these findings and guide future policy on IVIG treatment in Thailand.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

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