FACTORS AFFECTING THE CLINICAL OUTCOME OF PEDIATRIC ANTI- N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS, A SINGLE CENTER STUDY

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ABSTRACT

Background: Anti-N-Methyl-D-Aspartate receptor (anti-NMDAR) Encephalitis is the most common type of autoimmune encephalitis that affects children, adolescents and young adults. Since its discovery in 2007, there is still a paucity of data on the disease and factors affecting its outcome.

Objectives: To describe the clinical characteristics of children and adolescents with anti-NMDAR encephalitis and to analyze factors that may affect its outcome.

Methods: Forty-three patient records of diagnosed anti-NMDAR Encephalitis were included. The outcome was evaluated using the modified Rankin Scale (mRS), and Clinical Assessment Scale for autoimmune Encephalitis (CASE).

Results: Ages ranged from 2 years to 18 years old, majority in the 12-18 years age range. Sixty percent were female. First line treatment using immunotherapy was given to all patients: 37% as monotherapy and 84% combination therapy (MPT only 23%, IVIg only 4%, MPT + IVIg or TPE 21-26%, and MPT + IVIg + TPE 16%). Clinical outcomes on discharge and on follow-up were assessed using the mRS and CASE. On discharge the proportion of the patients who had mild impairment (mRS<2, CASE<9) was more than 50%. On median duration follow-up of 31 weeks (range 24-40 weeks), 96.8% had significant improvement (mRS<2, CASE<9). Among the possible factors that were assessed to affect outcome, only severity of the illness at the start of the treatment influenced clinical outcome.

Conclusion: Early diagnosis and initiation of treatment before the progression of the disease will promote faster recovery and more optimal clinical outcome. CASE may be used as an additional tool in assessing response to treatment.

Keywords: Anti-NMDAR encephalitis, autoimmune

INTRODUCTION

Autoimmune encephalitis (AE) is a clinical spectrum of neuropsychiatric symptoms such as deficits of memory, cognition, psychosis, seizures, abnormal movements, or coma. The most common type is the anti-N-methyl-D-aspartate (NMDA) receptor encephalitis surpassing viral encephalitis. [2] Anti-N-Methyl-D-Aspartate receptor (anti-NMDAR) encephalitis affects predominantly young adults, adolescents, and children as young as 22 months of age. A female preponderance has been observed (Female:Male:4:1).[1,3,6,7,8] Prodromal symptoms such as headache, fever, or a viral-like illness, can precede the neuropsychiatric symptoms in about 1/3 of cases.[4] The disease course is variable in the pediatric age group, and is severe especially if diagnosed late, requiring prolonged hospitalization and intensive treatment. Studies have shown that early initiation of treatment often leads to better outcome, but even in those patients with delayed diagnosis and treatment, immunotherapy could still result in significant clinical improvement. [12,13] At present, the modified Rankin Scale (mRS) has been used to assess the outcome of patients with autoimmune encephalitis, including anti-NMDAR encephalitis both in adults and children. It is, however, a non-specific tool that assesses the functional outcome and degree of disability of the patients. A more specific assessment tool that assesses more impairment can provide a better profile of the clinical outcome.

In 2019, Lim et al, presented a new and more specific Clinical Assessment Scale for autoimmune encephalitis (CASE) consisting of nine (9) items (seizure, memory dysfunction, psychiatric symptoms, consciousness, language problems, dyskinesia/dystonia, gait instability, and ataxia, brainstem dysfunction, and weakness) which was further validated in a multicenter validation cohort study.[16] Using this tool, Shim (2020) investigated the clinical features and long-term outcomes of 32 children with anti-NMDAR encephalitis aged 7 months - 17 years old, and compared the results with the mRS scores. While

the mRS scores showed good functional outcome in the majority of the patients, the results of the CASE assessment tool showed that these patients continued to have significant impairments in the cognitive and memory abilities. In the present study, the clinical features, and outcomes of 43 pediatric anti-NMDAR encephalitis patients were evaluated using both the mRS and CASE.

General Objective

To determine the clinical outcomes of pediatric patients diagnosed with Anti-NMDAR Encephalitis admitted at Philippine Children's Medical Center from 2018-2020, and the factors that affect these clinical outcomes.

Specific Objectives

1. Describe the baseline characteristics of the patients based on:
    a. Demographics
        i. Age at onset of illness
        ii. Gender
        iii. Geographic Location
        iv. Duration of illness before the diagnosis
        v. Duration of illness before the initiation of treatment
    b. Clinical Profile
        i. Symptomatology: Prodrome, Initial symptoms, Symptoms from the time of admission until discharge
        ii. Diagnostics
            1. Electroencephalogram (EEG)
            2. Cerebrospinal Fluid (CSF) Analysis
            3. Neuroimaging (Cranial Computed Tomography (CT) Scan and Magnetic

Resonance Imaging (MRI)

4. Tumor work-up

2. Classify the patients based on the severity of the symptoms using CASE and mRS prior to initiation of treatment.
3. Determine the response to treatment either with Monotherapy (Methylprednisolone (MPT) or Intravenous Immunoglobulin (IVIg); and Combination therapy (MPT + IVIg, MPT + TPE, MPT + IVIg + TPE) upon discharge and on follow-up (within 6 months) using CASE and mRS.
4. Determine if age, severity of illness based on mRS and CASE, and duration of illness prior to initiation of treatment will affect their response to treatment.
5. Identify the adverse effects or events during and after treatment.

METHODOLOGY

This was a retrospective cohort Study of patients confirmed with anti-NMDAR Encephalitis admitted at Philippine Children's Medical Center from January 2018 until December 2020. A minimum of 40 patients diagnosed with anti-NMDAR encephalitis was required to have an 80% chance of determining, as significant at the 5% level, the changes in response to treatment according to age at onset, severity of illness, type of treatment and duration of illness before treatment based on assumed large effect sizes.

Inclusion

- *All patients with a clinical diagnosis of definite anti-NMDAR Encephalitis*
- *Admitted and given immunotherapy: Monotherapy with MPT or IVIg; or Combination therapy with (MPT + IVIg, MPT + TPE, MPT + IVIg + TPE)*
- *Age 1 to 18 years old*

Exclusion

- *Patients with anti-NMDAR encephalitis admitted for another medical condition/systemic illness*

- *Patients with anti-NMDAR encephalitis who did not receive treatment*

This study reviewed both in-patient and out-patient records of all patients diagnosed with Anti-NMDAr Encephalitis from January 2018 until December 2020. Forty-eight charts were retrieved and 43 were included based on the inclusion criteria. Three of the excluded subjects did not receive any treatment and went home against medical advice, and two were seen as out-patient only.

A standardized three-part data collection tool was used. Part I consisted of the general and clinical data of the patients including the mRS scores. Part II was the assessment of severity of symptoms using the CASE, and Part III included the adverse effects of treatment. This study determined the factors affecting the outcomes based on age, severity and type of treatment, using the CASE and mRS. Outcome of patients was described as GOOD (mRS 0-2 or CASE score of 0-9) or POOR (mRS 3-5 or CASE score of 10 or more). Recovery from illness was described as follows: Full Recovery (mRS 0 or CASE Score of 0); Substantial improvement (mRS 1-2 or CASE 1-9); Limited Recovery (mRS 3-5 or CASE 10 – 18). mRS of 6 or CASE of 20 indicated death from the illness. Summary statistics were reported as mean and standard deviation (SD) or standard error (SE) for continuous data with normal distribution or as median (range) for quantitative variables with skewed distribution and as count (percent) for qualitative measures. Shapiro-Wilks test was used to determine whether continuous variables deviate from a normal (Gaussian) distribution. McNemar test was used to compare proportion of patients according to symptoms across periods of assessment. Analysis of variance of repeated measures was used to estimate how treatment response based on total CASE score changed according to type of treatment, age at onset, severity of illness and duration of illness before treatment. Kruskal Wallis test was used to compare treatment response based on mRS scores. Friedman test was used to compare treatment response based on mRS scores across

periods of assessment. Mann Whitney U test was used to compare mRS scores between severity of illness (mRS) and duration of illness before treatment. Chi-square test or Fisher's exact test was used to compare proportions. Pairwise comparisons of proportions were based on Bonferroni adjusted *p*-values. Kaplan-Meier analysis was performed to estimate mean time to achieving good treatment response and full recovery. Log rank test was used to compare time across treatments. Bivariate cox proportional hazards regression analysis was performed to assess possible effects of age at onset, severity and duration of symptoms prior to initiation of treatment on treatment response. Multivariate models were derived where possible. Crude and adjusted hazards ratio and 95% confidence interval were reported. One-way analysis of variance was used to compare duration of illness at follow-up across treatment. Statistical significance was based on p-value ≤ 0.05. STATA version 15 (Stata Corp LLC, College Station, TX, US) was used in data processing and analysis.

RESULTS

Forty-three patients were included in this study. Table 1 shows the baseline characteristics of patients. The majority were female (60.5%) in adolescence (55.8%), with a duration of illness of 1-3 months (58%) before initiation of treatment. Prodromal symptoms were seen in 39.5%, [headache (20.9%), fever (11.6%) and respiratory illness (14%)]. Tumor workups were all negative. Brain imaging was abnormal in 7%. CSF analysis was abnormal in 11 patients (25%) which included lymphocytic pleocytosis and elevated CSF protein levels. Thirty-two EEG studies were available for review. Eighty seven percent were abnormal [generalized slowing (46.4%), continuous delta slowing (53.5%) focal slowing (75%), epileptiform discharges (7.14%) and delta brush (7.14%)].

Table 1. Baseline characteristics of patients n=43

Characteristic	No. of Patients (Percent)
Age in years	
Early childhood (2 years to 5 years old)	8 (18.6%)
Middle childhood (6 years to 11 years old)	11 (25.6%)
Adolescence (12 years to 18 years old)	24 (55.8%)
Gender	
Male	17 (39.5%)
Female	26 (60.5%)
Location	
Within Metro Manila	17 (39.5%)
Outside Metro Manila	26 (60.5%)
Duration of illness prior to admission (in months)	
<1	37 (86.0%)
1-3	6 (14.0%)
Duration of illness before treatment (in months)	
<1	18 (41.9%)
1-3	25 (58.1%)
Prodrome	
At least one symptom	17 (39.5%)
Fever	5 (11.6%)
Headache	9 (20.9%)
Respiratory	6 (14.0%)
Ultrasound (Abdominal,Pelvic,Testicular)	
Normal	41 (95.3%)
Abnormal	2 (4.7%)
Cranial MRI/CT scan	
Normal	40 (93.0%)
Abnormal	3 (7.0%)
CSF White blood cell count	
Normal (≤ 5 cells/hpf)	39 (90.7%)
Elevated (> 5 cells/hpf)	4 (9.3%)
CSF protein level in mg/L	
≤450	36 (83.7%)
>450	7 (16.3%)
Electroencephalogram (n=32)	
Normal	4 (12.5%)
Abnormal EEG*	28 (87.5%)
Generalized background slowing	13(46.4%)
Continuous delta slowing	15 (53.5%)
Intermittent Focal slowing	21 (75%)
Frontal	9 (32.14%)
Frontotemporal	9 (32.14%)
Midtemporal	4 (14.28%)
Temporal	4 (14.28%)
Occipital	2 (7.14%)
Frontocentral	6 (21.42%)
Centroparietal	3 (10.71%)
Focal epileptiform activity	2 (7.14%)
Delta brush	2 (7.14%)

Characteristic	No. of Patients (Percent)
Electromyography (n=5)	
Normal	2 (40%)
Abnormal	3 (60%)
Treatment regimen	
Monotherapy	16 (37%)
MPT	14 (23%)
IVIg	2 (4.65%)
Combination	
MPT + IVIg	10 (26%)
MPT + TPE	9 (21%)
MPT+ IVIg +TPE	8 (16%)

Data are n (%) on 43 pediatric patients with anti-NMDAR encephalitis.

CT: computed tomography, MRI: magnetic resonance imaging, CSF: cerebrospinal fluid

Table 2. Treatment regimen given to Filipino children with anti-NMDAR encephalitis (n=43)

Treatment regimen	Number of patients (n=43)
Monotherapy	16 (37%)
MPT	14 (23%)
IVIg	2 (4.65%)
Combination	
MPT + IVIg	10 (26%)
MPT + TPE	9 (21%)
MPT+ IVIg +TPE	8 (16%)

Initial symptoms reported at the time of admission (Figure 1) included seizures (51.2%), cognitive and behavioral impairments (37.2%), sleep disorders (9.3%), movement disorders (4.7%) and language problems (2.3%). Post-treatment, there was a significant decrease in the number of patients with seizures (9.3% vs. 67.4%), movement disorder (53.5% vs. 72.1%) and language deficits (65.1% vs. 90.7%). A further decrease in the proportion of patients with movement disorders was observed upon discharge (11.9% vs. 52.4%, n=42). On follow-up (range: 20-40 weeks, median 31 weeks), cognitive and behavioral impairments were still present in 41.9% of patients. One patient did not show any functional improvement.

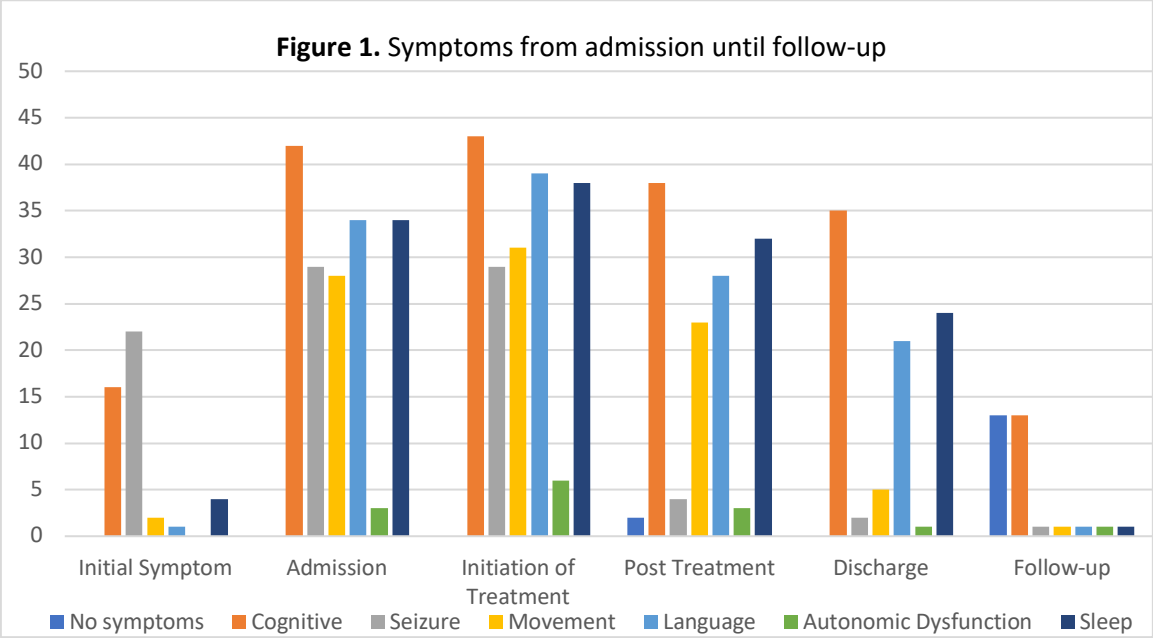

Fig 1. Distribution of patients based on the severity of symptoms using mRS and CASE

Figure 2 presents the severity of symptoms based on mRS and CASE scores prior to initiation of treatment. Based on mRS 79.1% had moderate and 20.9% had severe symptoms. Using the total CASE scores, symptoms were either mild (14%), moderate (58.1%) or severe (27.9%).

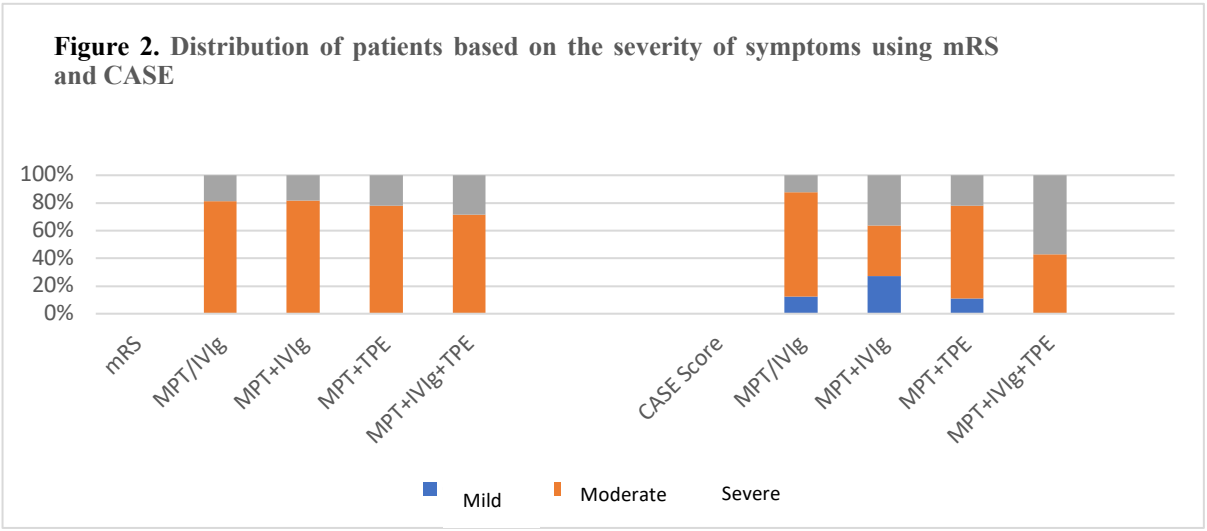

Fig 2. Response to treatment according to type of treatment and period of assessment

Overall, there was a difference in the mRS and CASE scores from initiation of treatment until follow-up. However, the scores at each period of assessment were comparable across the treatment groups (Figure 3).

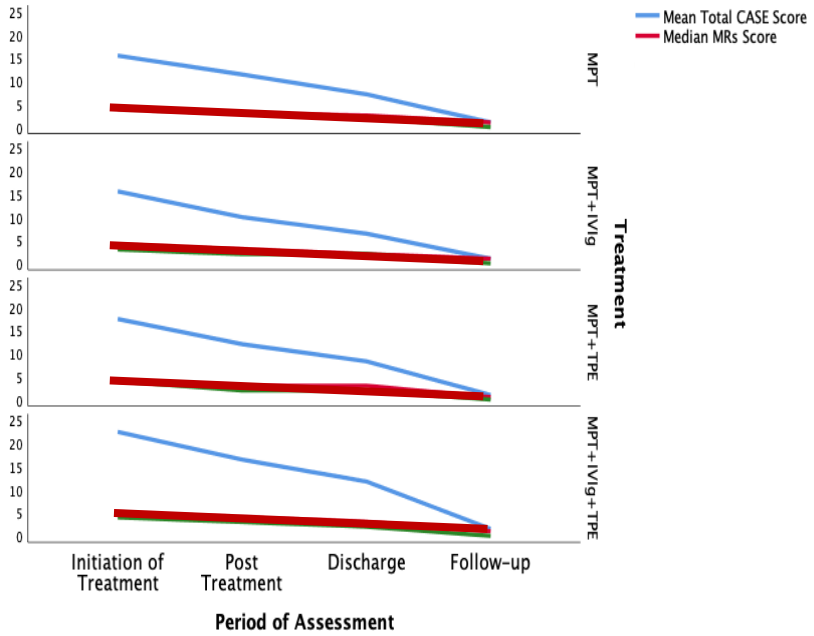

Figure 3. Total CASE and mRS scores from initiation of treatment to follow-up

The response to treatment on discharge (Table 3) and follow-up (Table 4) was analyzed using the mRS, and CASE score.

Table 3. Response to treatment as measured by mRS score, CASE on discharge

		Severity			Time to Mild Symptoms (in weeks)		
Treatment	No. of Patients	Mild	Moderate	Severe	Mean	SE	95% CI
mRS							
Monotherapy + MPT/IVG	15	8 (53.3%)	7 (46.7%)	-	6.375	0.614	5.171 to 7.579
MPT + IVIg	11	8 (72.7%)	3 (27.3%)	-	6.916	0.573	5.793 to 8.040
MPT + TPE	9	4 (44.4%)	5 (55.6%)	-	7.356	0.486	6.403 to 8.309
MPT + IVIg + TPE	7	3 (42.9%)	3 (42.9%)	1 (14.3%)	10.918	1.894	7.206 to 14.631
Total	42	23 (54.8%)	18 (42.9%)	1 (2.4%)	9.076	0.797	7.514 to 14.631
CASE Score							
Monotherapy + MPT/IVG	15	11 (73.3%)	4 (26.7%)	-	5.670	0.545	4.601 to 6.739
MPT + IVIg	11	8 (72.7%)	3 (27.3%)	-	6.879	0.594	5.714 to 8.043
MPT + TPE	9	6 (66.7%)	3 (33.3%)	-	7.265	0.544	6.198 to 8.331
MPT + IVIg + TPE	7	4 (57.1%)	2 (28.6%)	1 (14.3%)	10.612	1.796	7.093 to 14.132
Total	42	29 (69.0%)	12 (28.6%)	1 (2.4%)	7.845	0.676	6.519 to 9.170

MRS data are n (%), mean time, standard error and 95% confidence interval on 42 pediatric patients with anti-NMDAR encephalitis. One patient expired post MPT treatment. CASE Data are n (%), mean, standard error and 95% confidence interval on 42 pediatric patients with anti-NMDAR encephalitis. One patient expired post MPT treatment.

Table 4. Response to treatment as measured by mRS score, CASE **on follow-up**

Treatment		Severity			Time to No or Mild Symptoms (in weeks)		
	No. of Patients	No Symptom	Mild	Severe	Mean	SE	95% CI
MRS							
Monotherapy + MPT/IVG	9	4 (44.4%)	5 (55.6%)	-	31.825	0.675	30.502 to 33.148
MPT + IVIg	8	1 (12.5%)	7 (87.5%)	-	33.286	0.722	31.871 to 34.701
MPT + TPE	7	3 (42.9%)	4 (57.1%)	-	34.143	0.296	33.563 to 34.723
MPT + IVIg + TPE	7	3 (42.9%)	3 (42.9%)	1 (14.3%)	35.755	1.493	32.830 to 36.681
Total	31	11 (35.5%)	19 (61.3%)	1 (3.2%)	33.613	0.498	32.636 to 34.589
CASE Score							
Monotherapy + MPT/IVG	9	2 (22.2%)	7 (77.8%)		32.219	0.864	32.525 to 35.913
MPT + IVIg	8	3 (37.5%)	5 (62.5%)		24.564	0.870	32.860 to 36.269
MPT + TPE	7	2 (28.6%)	5 (71.4%)		34.449	0.330	33.803 to 35.095
MPT + IVIg + TPE	7	1 (14.3%)	6 (85.7%)		40.000	1.608	36.848 to 43.152
Total	31	8 (25.8%)	23 (74.2%)		38.609	0.944	36.759 to 40.458

MRS and CASE Score Data are n (%), mean time, standard error and 95% confidence interval on 31 pediatric patients with anti-NMDAR encephalitis.

The mean time to determine improvement to mild symptoms was 9.076 weeks (SE=0.797, 95% CI: 7.514 to 10.631) using mRS scores and 7.825 weeks using the CASE score. Using mRS 54.8% (95% CI: 38.7% to 70.2%) improved with mild symptoms (mRS 0-2) and 45.2% (95% CI=29.8^ to 61.3%) with moderate to severe symptoms (mRS 3-5) at the time of discharge. Using the CASE score, 69% (95% CI: 52.9% to 82.4%) had mild symptoms (good response) and 31% (95% CI=17.6% to 47.1%) had moderate to severe symptoms (poor response) on discharge. None had full recovery on discharge. Comparing these data to the pre-treatment severity of symptoms, most of the patients improved from either severe to moderate symptoms to mild and moderate

symptoms, with 1 exception. Comparison across treatment modalities, however, showed insufficient evidence of significant differences in severity (mRS p=0.469) (CASE p=0.905) and time to good outcome or mild symptoms (mRS p=0.252) (CASE p=0.114).

Only 31 patients were seen on follow-up. Follow-up ranged from 20-40 weeks (median 31 weeks). The mRS (0-2) on follow-up was 96.8% (95% CI: 83.3% to 99.9%) indicating good response to treatment; 61.3% had mild symptoms and 35.5% had no symptoms (full recovery). The mean time to full recovery was 33.6 weeks (SE=0.498, 95% CI: 32.636 to 34.589). The patients who had mild symptoms on follow-up received either monotherapy (55.6%), and combination therapy (44.4%). Based on the CASE score all patients had favorable response to treatment. There were 25.8% (95% CI: 11.9% to 44.6%) who had full recovery (no symptoms) and 74.2% (95% CI: 55.4% to 88.1%) had mild symptoms, with a mean time to full recovery of 38.6 weeks (SE=0.944, 95% CI: 36.759 to 40.458). Comparison across treatment, however, showed insufficient evidence of significant differences in severity of symptoms (mRS p=0.452) (CASE p=0.856) and time to full recovery across treatment modalities (CASE p=0.664) on follow-up.

Factors associated with response to treatment on discharge and follow-up using the mRS are shown in Table 5 and 6 respectively. There was a significant crude association between severity of symptoms prior to treatment and achieving a good treatment response, as patients with moderate symptoms prior to treatment achieved good treatment response faster than those with severe symptoms (crude HR=11.488, 95% CI: 1.504 to 87.751, p=0.019). However, there was insufficient evidence that age at onset, severity and duration of illness prior to treatment had significant effects on achieving full recovery at follow-up.

Table 5. Response to treatment on discharge using mRS

Factor	Patients with Good Response	Patients with Poor Response	Crude HR (95% CI	*p*-value
Treatment				
Monotherapy + MPT/IVG	8 (34.8%)	7 (36.8%)	2.868 (0.741, 11.096)	0.127
MPT + IVIg	8 (34.8%)	3 (15.8%)	2.206 (0.583, 8.349)	0.244
MPT + TPE	4 (17.4%)	5 (26.3%)	1.119 (0.250, 5.018)	0.883
MPT + IVIg + TPE	3 (14.0%)	4 (21.1%)	1	
Age at onset in years				
Early childhood	4 (17.4%)	4 (21.1%)	1.146 (0.364, 3.612)	0.816
Middle childhood	8 (34.8%)	3 (15.8%)	1.371 (0.547, 3.433)	0.501
Early adolescent	11 (47.8%)	12 (63.2%)	1	
Severity of illness before treatment (mRS)				
Moderate	**22 (95.7%)***	**12 (63.2%)**	**11.488 (1.504, 87.751)**	**0.019§**
Severe	**1 (4.3%)***	**7 (36.8%)**	**1**	
Duration of illness before treatment in months				
<1	9 (39.1%)	8 (42.1%)	1.111 (0.479, 2.576)	0.806
1-3	14 (60.9%)	11 (57.9%)	1	

Data are n (%), hazard ratio and 95% confidence interval on 42 pediatric patients with anti-NMDAR encephalitis. * P<0.05 vs. patients with poor response, § P<0.05 vs. reference category

Table 6. Response to treatment at follow-up using mRS

Factor	Patients with Full Recovery	Patients without Full Recovery	Crude HR (95% CI)	*p*-value
Treatment				
Monotherapy + MPT/IVG	4 (36.4%)	5 (25.0%)	3.288 (0.581, 18.614)	0.178
MPT + IVIg	1 (9.1%)	7 (35.0%)	0.535 (048 to 5.917)	0.610
MPT + TPE	3 (27.3%)	4 (20.0%)	1.318 (0.219 to 7.925)	0.763
MPT + IVIg + TPE	3 (27.3%)	4 (20.0%)	1	
Age at onset in years				
Early childhood	2 (18.2%)	3 (15.0%)	1.104 (0.213, 5.716)	0.906
Middle childhood	3 (27.3%)	6 (30.0%)	1.007 (0.239, 4.248)	0.992
Early adolescent	6 (54.5%)	11 (55.0%)	1	
Severity of symptoms before treatment (mRS)				
Moderate	**10 (90.9%)**	**13 (65.0%)**	**7.447 (0.913, 60.702)**	**0.061**
Severe	**1 (9.1%)**	**7 (35.0%)**	**1**	
Duration of illness before treatment in months				
<1	4 (36.4%)	8 (40.0%)	1	
1-3	7 (63.6%)	12 (60.0%)	1.122 (0.327, 3.853)	0.855

Data are n (%), hazard ratio and 95% confidence interval on 31 pediatric patients with anti-NMDAR encephalitis with at least 80 days follow-up.

Factors associated with response to treatment at discharge and follow-up using the CASE score are shown in Table 7 and 8 respectively. The type of treatment and severity of symptoms prior to initiation of treatment had significant crude associations to achieving a good treatment response (no or mild symptoms). That is, patients who received monotherapy with MPT or IVG were more likely to achieve good treatment response faster than those treated with a combination of MPT, IVIg and TPE. Similarly, those with mild or moderate symptoms prior to treatment were more likely to achieve good treatment response faster than those with severe symptoms. Severity of symptoms prior initiation of treatment had a crude association with achieving full recovery. Those with mild symptoms prior to treatment were more likely to recover faster than those with severe symptoms (crude HR=12.907, 95% 1.416 to 117.682, p=0.023)

Table 7. Response to treatment at discharge according to treatment, age at onset of illness, duration, and severity of illness prior to initiation of treatment

Factor	Patients with Good Response	Patients with Poor Response	Model 1	
			Adjusted HR (95% CI)	*p*-value
Treatment				
Monotherapy + MPT/IVG	11 (37.9%)	4 (30.8%)	2.661 (0.700, 10.111)	0.151
MPT + IVIg	8 (27.6%)	3 (23.1%)	2.441 (0.616, 9.678)	0.204
MPT + TPE	6 (20.7%)	3 (23.1%)	1.298 (0.309, 5.449)	0.722
MPT + IVIg + TPE	4 (13.8%)	3 (23.1%)	1	
Age at onset in years				
Early childhood	5 (17.2%)	3 (23.1%)		
Middle childhood	8 (27.6%)	3 (23.1%)		
Early adolescent	16 (55.2%)	7 (53.8%)		
Severity of symptoms before treatment (CASE)				
Mild	**6 (20.7%)**	**-**	**3.680 (1.025, 13.213)**	**0.046§**
Moderate	**18 (62.1%)**	**6 (46.2%)**	**2.878 (0.948, 8.739)**	**0.062§**
Severe	**5 (17.2%)***	**7 (53.8%)**		
Duration of illness before treatment in months				
<1	10 (34.5%)	7 (53.8%)		
1-3	19 (65.5%)	6 (46.2%)		

Data are n (%), hazard ratio and 95% confidence interval on 42 pediatric patients with anti-NMDAR encephalitis. Treatment response was classified as either good (no symptoms or mild) or poor (moderate to severe symptoms). Model 1 is a multivariate model on treatment and age.
* P<0.05 vs. poor response. § P<0.05 vs. reference category

TABLE 8. Response to treatment at follow-up according to treatment, age at onset of illness, duration and severity of illness prior to initiation of treatment

Factor	Patients with Full Recovery	Patients without Full Recovery	Crude HR (95% CI)	*p*-value
Treatment				
Monotherapy + MPT/IVG	2 (25.0%)	7 (30.4%)	3.635 (3.23, 40.965)	0.296
MPT + IVIg	3 (27.5%)	5 (21.7%)	3.101 (0.322, 29.879)	0.328
MPT + TPE	2 (25.0%)	5 (21.7%)	1.798 (0.162, 19.919)	0.622
MPT + IVIg + TPE	11 (12.5%)	6 (26.1%)	1	
Age at onset in years				
Early childhood	1 (12.5%)	4 (17.4%)	0.709 (0.079, 6.368)	0.759
Middle childhood	3 (37.5%)	6 (26.1%)	1.226 (0.271, 5.548)	0.791
Early adolescent	4 (50.0%)	13 (56.5%)	1	
Severity of illness before treatment (CASE)				
Mild	4 (50.0%)*	2 (8.7%)	12.907 (1.416, 117.682)	0.023§
Moderate	3 (37.5%)	11 (47.8%)	3.238 (0.336, 31.248)	0.310
Severe	1 (12.5%)	10 (43.5%)	1	
Duration of illness before treatment in months				
<1	5 (62.5%)	7 (30.4%)	1	
1-3	3 (37.5%)	16 (69.6%)	0.392 (0.093, 1.656)	0.203

Data are n (%), hazard ratio and 95% confidence interval on 31 pediatric patients with anti-NMDAR encephalitis with at least 80 days follow-up.
* P<0.05 vs. patients without full recovery. § P<0.05 vs. reference category

Three patients (7.1%) developed intravenous catheter-related-infection while ongoing treatment. One patient expired post-monotherapy treatment due to severe autonomic dysfunction.

DISCUSSION

This study retrospectively analyzed the clinical and paraclinical factors of the 43 patients diagnosed with anti-NMDAR encephalitis and their response to immunotherapy. Overall, anti-NMDAR encephalitis has been reported across all age groups, mostly affecting female children and young adults.[1,3,4,6] These results were consistent in this study, where 60.5% were females belonging to the early adolescent group. The association of paraneoplastic syndromes in the form of ovarian tumors and anti-NMDAR encephalitis has been established by Zhang et al. [19] However, all tumor workups turned out negative in this study. Although, recommended screening for tumors should be done every 6 months, as the incidence of paraneoplastic syndromes increases with age.

In children, a prodrome or viral illness 1-2 weeks before the onset of neuropsychiatric symptoms has been associated with the seasonal variability of anti-NMDAR encephalitis. Interestingly, this study found that 17 (39.5%) patients who presented with a prodrome had onset of symptoms within the flu season, including 8 (18.6%) with headache, 4 (9.3%) respiratory symptoms, 2 (4.6%) fever, and the remaining three 3 (6.9%) had a combination of either fever and headache or fever and respiratory symptoms. Post-viral association with herpes simplex virus was also seen in some patients.[21] In this study, all patients who had CSF analysis were all negative. In this study, the initial neuropsychiatric symptoms were consistent with those described by Dalmau.[22] These include seizures (51.2%), cognitive and behavioral dysfunction (37.2%), sleep alteration (9.3%), abnormal movement (4.7%)

and language alterations (2.3%). Due to these symptoms, a few were initially treated as cases of new-onset epilepsy, viral encephalitis, and psychiatric disorders causing delays in diagnosis and treatment. During the illness, there was a significant increase in the proportion of patients with symptoms of cognitive dysfunction (97.7% vs. 37.2%), sleep disturbance (79.1% vs. 9.3%), and movement disorder (65.1% vs. 4.7%). This pattern of symptom progression was also described by Dalmau in 2017. [1,22] Consistent with an Italian multicenter study on pediatric patients in 2014 [23-25] this study revealed that seizure was the most common initial presentation during the acute phase of illness of patients regardless of gender and age, usually presenting as generalized onset seizures, and some cases as status epilepticus. Cognitive dysfunction (37.2%) was the second most common initial presentation. A systematic review of anti-NMDAR encephalitis patients in Australia reported high rates of persistent impairments in the executive functioning and episodic memory on discharge. These deficits may be explained by abnormalities in the hippocampus and frontal lobes. This same study found that early treatment was the most important clinical factor favoring good cognitive outcome.[28] Monitoring of cognitive functions in the younger age group can be difficult.

All 43 patients had positive anti-NMDAR antibody test on CSF, other abnormal findings include pleocytosis in 9.3% and elevated protein in 16.3%. In some studies, these abnormal CSF findings are reported in as many as 80% of cases. However, these findings have not been shown to affect the outcome of patients.[25] Ninety percent of the imaging studies done were normal, and a handful had non-specific punctate white matter changes. These findings were consistent with the findings of Titulaer.[4,5] mRS and CASE were used to measure the clinical outcome of patients. A dramatic decrease in

the severity of symptoms from moderate or severe to mild was observed on discharge in the majority of patients, regardless of the treatment given. The results revealed a faster recovery among those who received Methylprednisolone alone, or in combination with IVIg, as these patients were the ones who had the less severe symptoms upon initiation of treatment. The final outcome of 31 patients who followed up for a mean duration of 31 weeks was also reviewed. The clinical outcome review revealed that 11% had full recovery, while 89% had substantial recovery. However, looking at the CASE scores of these patients, despite the good outcome, most still have neurocognitive deficit. Since CASE may have an advantage over mRS in tracking the recovery of each symptom of pediatric anti-NMDAR encephalitis, it could be preferentially used in pediatric anti-NMDAR encephalitis. Among all the factors analyzed, the severity of symptoms at the time of initiation of treatment had the most impact in the outcome of the patients.

Several limitations of the present study should be addressed in future studies. First, since this was a retrospective study, there was limitation in the quality of clinical data that could be assessed. Second, since the CASE score was determined retrospectively based on medical records, its clinical utility and accuracy could not be determined. Third, since formal neurocognitive function testing was not performed on follow-up we are unable to conclude whether CASE scoring can identify pediatric patients at risk for neuropsychological problems.

CONCLUSIONS AND RECOMMENDATIONS

This study provided data about the clinical features and factors affecting the outcomes among 43 pediatric anti-NMDAR encephalitis patients based on mRS and CASE. Although the study results are generally consistent with previous findings, our study suggests that the severity of illness prior to initiation of

treatment played an important role in the prognosis, response to treatment, and outcome. Hence, the importance of early diagnosis and treatment in preventing morbidity and mortality in patients cannot be over emphasized. Despite the overall favorable outcomes, cognitive problems may still persist even on follow-up. CASE as another assessment tool may be used to detect these neurocognitive deficits and help in appropriate management. Finally, an appropriate diagnostic and treatment algorithm should be established to facilitate early diagnosis and management. A prospective design with larger sample size is recommended to make correlations between other clinical factors and outcomes. We suggest a prospective, multi-center design using the CASE scoring system, with formal neurocognitive function testing, to overcome these limitations.

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