

# Clinical Spectrum, Treatment and Outcome of Children with Autoimmune Encephalitis

Mohammad Raza, Khairunnisa Mukhtiar and Shahnaz Ibrahim

Department of Paediatrics and Child Health, Section of Paediatric Neurology, The Aga Khan University Hospital, Karachi, Pakistan

## ABSTRACT

**Objective:** To assess the clinical spectrum, treatment, and outcome of children with autoimmune encephalitis (AE).

**Study Design:** Descriptive study.

**Place and Duration of the Study:** Department of Paediatrics, The Aga Khan University Hospital, Karachi, Pakistan, from January 2017 to December 2021.

**Methodology:** Medical records of children with a diagnosis of AE were reviewed for clinical features, treatment details, and outcomes. Outcome was defined as good (0-2) or poor (3-6) based on a modified Rankin Scale (mRS) score at 3-month follow-up. Descriptive statistics were reported and logistic regression was used to assess the prognostic factors associated with outcome.

**Results:** Thirty-three patients were identified with AE. Thirteen (39.3%) were antibody positive. Anti-N-methyl-D-aspartate receptor (NMDAR) antibody was seen in 92% of positive cases. Behavioural abnormalities (87.8%), seizures (81.8%), movement disorders (66.6%), psychiatric symptoms (63.6%), and mutism (33.3%) were the prominent symptoms. Thirty (91%) patients received first-line immunotherapy. Good outcome was seen in 14 (48.2%) patients. Univariable analysis showed that the odds of having poor outcome were 2.5 (95% confidence interval [CI] 0.37-16.88,  $p=0.34$ ) in patients with chorea. In addition, an elevated cerebrospinal fluid (CSF) protein had an odds ratio (OR) of 8.6 (CI 0.88-84.83,  $p=0.064$ ) and positive CSF antibodies had an OR of 3.7 (CI 0.79-17.72,  $p=0.095$ ) for a poor outcome. Mortality was seen in 4 (12.1%) patients.

**Conclusion:** A very low threshold is needed for the diagnosis of AE in children presenting with behavioural symptoms and chorea. Although the odds for poor prognosis were higher in patients with chorea, elevated CSF protein and positive CSF antibodies, the  $p$ -value did not come out significant.

**Key Words:** Autoimmune encephalitis, Antibodies, NMDAR, Immunotherapies, mRS score, Outcome.

**How to cite this article:** Raza M, Mukhtiar K, Ibrahim S. Clinical Spectrum, Treatment and Outcome of Children with Autoimmune Encephalitis. *J Coll Physicians Surg Pak* 2024; **34(03)**:323-328.

## INTRODUCTION

Autoimmune encephalitis (AE) is a spectrum of immune-mediated encephalopathies, involving brain parenchyma.<sup>1</sup> AE is closely associated with antibodies directed against neuronal cell-surface antigens, the common antigens include NMDAR, AMPAR, GABAAR/BR, DPPX, LGI1, and CASPR2.<sup>1,2</sup> Some patients have seronegative disease, a variant with unidentified antibodies.<sup>1</sup> The most common form of antibody-mediated AE is anti-NMDAR encephalitis. Forty per cent of NMDAR encephalitis cases occur in patients younger than 18 years.<sup>2</sup> The prevalence rate of AE reported in recent literature is 13.7/100,000 in the USA.<sup>1</sup> Common presentations are acute or subacute neuropsychiatric symptoms, seizures, confusion, agitation, impaired consciousness, sleep disturbance, cognitive impairment, and movement disorder.<sup>2-4</sup>

Seizures and movement disorders can be sometimes refractory to treatment.<sup>4</sup> Behavioural and psychiatric symptoms are common in AE and can vary from mild to fulminant.<sup>4</sup>

Delay in recognition and treatment of AE can result in poor prognosis and neurologic sequelae.<sup>4</sup> The diagnosis is based on certain specific criteria based not only on the clinical scenario and positive cerebrospinal (CSF) antibodies; supportive evidence of delta brushes on electroencephalogram (EEG) and magnetic resonance imaging (MRI) changes suggestive of encephalitis may help in diagnosis if antibodies are negative and in early initiation of treatment pending the antibody results.<sup>3,4</sup> The usual treatment approach involves first and second-line immunotherapies, treatment for seizures, and management of behavioural and psychiatric symptoms.<sup>2,3</sup> The outcome in NMDAR encephalitis is usually favourable and fewer relapses have been observed with early initiation of immunotherapy.<sup>3,5</sup> Good outcome is associated with early initiation of treatment, whilst risk factors for poor outcome include adult onset (>25 years), presentation with impaired consciousness, positive antibody, and  $\geq 50\%$  slow waves on EEG.<sup>6-11</sup>

AE is an increasingly recognised treatable disease and urgent treatment is associated with a better prognosis. Few case series

Correspondence to: Dr. Mohammad Raza, Department of Paediatrics and Child Health, Section of Paediatric Neurology, The Aga Khan University Hospital, Karachi, Pakistan

E-mail: dr.razamlk@gmail.com

Received: October 07, 2023; Revised: December 13, 2023;

Accepted: February 26, 2024

DOI: <https://doi.org/10.29271/jcpsp.2024.03.323>

have been reported from Pakistan<sup>12,13</sup> but with a small sample size containing adult as well as paediatric patients. The present analysis was done to better understand the clinical scenario and prognostic factors in children with AE. The objective of this study was to determine the clinical spectrum, treatment strategies, and outcome of children <18 years with AE.

## METHODOLOGY

The study was conducted at the Paediatric Department, The Aga Khan University Hospital, Karachi, Pakistan with retrospective data collection. Five-year records of all children < 18 years of age with a discharge diagnosis of AE (2017-2021) were evaluated. Children fulfilling the diagnostic criteria<sup>4</sup> of AE were included. Those diagnosed with a central nervous system (CNS) infection (based on CSF analysis, biofire film array and culture), metabolic encephalopathy (hepatic, uremic, electrolyte disturbance), drug intoxication or specific inherited metabolic/genetic disorder (e.g. urea cycle defect, organic acidemias, mitochondrial disorder) were excluded.

Ethical Review Committee (ERC) of the Agha Khan University Hospital approved the study, (ERC no: 2022-7685-22439). Medical records of participants were retrieved. Detailed information was collected regarding age, gender, and clinical symptoms including seizures (generalised, focal), cognitive dysfunction (behavioural change, confusion, aphasia), movement disorders (choreoathetosis, myoclonus, tremor), psychiatric disturbances (hallucinations, anxiety, agitation, mood disorders), sleep disorder, and dysautonomia. Investigations included CSF analysis, CSF biofire film array for viral/bacterial PCR, CSF culture, CSF autoantibodies (NMDA, AMPA, GABAAR/BR, DPPX, LGI1, and CASPR2 antigens), oligoclonal bands (paired with serum sample), EEG and MRI brain. The CSF autoimmune antibody assay was performed by indirect immunofluorescence staining method. Relevant transfected cells (against NMDA, AMPA, GABAAR/BR, DPPX, LGI1, and CASPR2) were reacted with control-transfected cells (EU-90) genetically transferred with nucleic acid (autoimmune encephalitis mosaic 6 kit). This standardised autoimmune antibody assay was performed on all the patients, using an undiluted CSF sample. Other workups included anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA) and screening for testicular/ovarian tumours. Treatment modalities were defined as first-line immunotherapy, second-line immunotherapy, and maintenance immunotherapy. First-line immunotherapy comprised of either methylprednisolone pulse therapy (30 mg/kg/day for 5 days), intravenous immunoglobulin (IVIG) 1g/kg/day for 2 days, plasmapheresis (total 5 sessions on alternate days) or combined therapy (steroids ± IVIG ± plasmapheresis). Rituximab (375 mg/m<sup>2</sup> weekly for 4 weeks) was used as second-line immunotherapy. Maintenance immunotherapy was given as oral prednisolone.

Outcome was assessed at a 3-month follow-up. Modified Rankin Scale (mRS) score<sup>14</sup> was done at 3 months to assess the functional status and to classify the outcome. Patients were categorised into two groups based on the main outcome, good

outcome (mRS score 0-2) or poor outcome (mRS score 3-6). Risk factors for poor outcome were studied including age, impaired consciousness, seizures, behavioural psychiatric disturbances, positive antibodies, EEG and MRI abnormalities, the interval between presentation and start of treatment, and the type of first-line treatment given.

All the statistical analyses were performed using statistical software Stata version 17.0. Mean ± SD was reported for the continuous variables while frequency with percentage was reported for the categorical variables, and median with IQR was reported for discrete variables (GCS score on arrival, duration of hospital stay, MRS score at admission, MRS score at discharge). Shapiro Wilcoxon test was used to assess the normality of variables. Chi-square or Fisher's exact test was used to check the association of categorical variables with the outcome, t-test was used for continuous variables, and the Wilcoxon rank-sum test was used for the discrete variables. Logistic regression was used at univariate level to check the predictors of outcome. Odds ratio with 95% CI was reported, all the factors with p < 0.10 were considered for the multivariate analysis. A final model was built using a stepwise backward elimination method and a p-value < 0.05 was considered statistically significant.

## RESULTS

Thirty-three patients of AE were included in this study. Out of them, thirteen (39.3%) were antibody-positive, while 20 (60.6%) were negative. Anti-N-methyl-D-aspartate receptor (NMDAR) antibody was the most common antibody seen in 92% of positive cases whilst one patient had a positive anti-contactin-associated protein-like 2 (CASPR2) antibody. Twenty (60.6%) of the patients were females. Mean age was 6.50±4.49 years. Fever was the most common prodromal symptom seen in 48.4% of patients. Common clinical manifestations were behavioural abnormalities (87.8%), seizures (81.8%), movement disorders (66.6%), psychiatric symptoms (63.6%), and mutism (33.3%). Generalised seizures were seen in 62.9% while 37% had focal seizures. Irritability (48.4%), confusion (12.1%), and amnesia (9%) were the common behavioural symptoms, while excessive crying, aggression and self-biting were seen in 1 (3%) each. Among the psychiatric symptoms, agitation was the commonest manifestation seen in 51.5% of patients whilst hallucinations, catatonia, mania, and schizophrenia were seen in 1 (3%) each. Chorea was the most common movement disorder (30.3%) followed by dystonia (12.1%), tremors (12.1%), and myoclonic jerks (6%). Details of clinical characteristics of patients are shown in Table I.

CNS infection was ruled out in all patients by doing CSF analysis, CSF culture and CSF herpes simplex virus (HSV) PCR. CSF protein was normal in 75% and high in 25% of children. CSF glucose was low in 40.6%, normal in 28.1% and high in 31.2% of patients. Four patients developed AE secondary to HSV encephalitis. Two patients developed it whilst receiving acyclovir as they developed orofacial dyskinesias and two patients developed it after completion of therapy.

**Table I: Clinical characteristics of study participants.**

Characteristics	Total (n=33)
<i>Clinical features and investigations</i>	
GCS score on arrival, Median (IQR)	14.00 (11.00-15.00)
Fever	16 (48.4%)
Behavioural changes	29 (87.8%)
Seizures	27 (81.8%)
Presentation with status epilepticus, n=27	6 (22.2%)
Psychiatric disturbances	21 (63.6%)
Movement disorder	22 (66.6%)
Dysautonomia	10 (30.3%)
Speech disturbance	
Mutism	11 (33.3%)
Dysarthria	2 (6.0%)
CSF Pleocytosis	16 (48.4%)
CSF specific oligoclonal bands	3 (9.0%)
Positive CSF neuronal antibodies	13 (39.3%)
Anti-NMDAR, n=13	12 (92.3%)
Anti-CASPR2, n=13	1 (7.6%)
CSF HSV PCR	
Negative	33 (100%)
CSF culture	
Negative	33 (100%)
Abnormal MRI findings	23 (69.7%)
Abnormal EEG	28 (84.8%)
Preceding history of HSV encephalitis	4 (12.1%)
<i>Treatment and Outcome</i>	
Need of mechanical ventilation, n=32	9 (28.1%)
Duration of hospital stay, days, median (IQR)	10.00 (7.00-16.00)
First-line immunotherapy received	30 (90.9%)
First-line medications, n= 30	
Pulse Methylprednisolone only	6 (20.0%)
IVIg only	7 (23.3%)
Pulse Methylprednisolone + IVIG	13 (43.3%)
Pulse Methylprednisolone +IVIG + Plasmapheresis	4 (13.3%)
Second-line immunotherapy received	3 (9.0%)
Maintenance immunotherapy (oral steroids) received	19 (57.5%)
MRS score at admission, Median (IQR)	5.00 (4.00-5.00)
MRS score at discharge, Median (IQR), n=32	4.00 (3.00-5.00)
Interval between presentation and start of treatment, days, n=30	3.50 (2.00-7.00)
Survived	25 (75.7%)
Expired	4 (12.1%)
Lost to follow-up	4 (12.1%)

GCS = Glasgow coma scale, CSF = Cerebrospinal fluid, NMDAR = N-methyl-D-aspartate receptor, CASPR2 = Contactin-associated protein-like 2, WBC = White blood cell, CBC = Complete blood count, NLR = Neutrophil to lymphocyte ratio, HSV = Herpes simplex virus, PCR = Polymerase chain reaction, MRI = Magnetic resonance imaging, EEG = Electroencephalogram, IVIG = Intravenous immunoglobulin, MRS = Modified Rankin scale.

**Table II: Comparison of clinical features and immunotherapy in good and poor outcome groups.**

Characteristics (Total N=29)	Good N=14 (48.27%)	Poor N=15 (51.73%)	p-value*
Age, years (mean ± SD)	7.29±3.29	5.60±5.25	0.31
<5 Years	2 (14.29%)	8 (53.33%)	0.068
5-10 Years	9 (64.29%)	4 (26.67%)	
>10 Years	3 (21.43%)	3 (20.00%)	
GCS score on arrival, median (IQR)	13.50 (12.00-15.00)	14.00 (10.00-15.00)	0.64
Seizures	11 (78.57%)	12 (80%)	0.92
Behavioural changes	13 (92.86%)	13 (86.67%)	0.58
Speech disturbance			0.3
Mutism	4 (28.57%)	6 (40.00%)	
Dysarthria	2 (14.29%)	0 (0.00%)	
Movement disorder	8 (57.1%)	12 (80%)	0.41
Psychiatric disturbances	9 (64.29%)	11 (73.33%)	0.6
CSF Protein*, n=32			0.039
Normal	13 (92.86%)	9 (60.00%)	
High	1 (7.14%)	6 (40.00%)	
CSF Glucose**, n=32			0.077
Low	3 (21.43%)	8 (53.33%)	
Normal	4 (28.57%)	5 (33.33%)	
High	7 (50.00%)	2 (13.33%)	
CSF Pleocytosis	6 (42.86%)	8 (53.33%)	0.57
CSF neuronal antibodies			0.089
Positive	4 (28.57%)	9 (60.00%)	
Negative	10 (71.43%)	6 (40.00%)	
Abnormal MRI findings	9 (64.29%)	10 (66.67%)	0.89
Abnormal EEG	12 (85.71%)	13 (86.67%)	0.94
Preceding history of HSV encephalitis	1 (7.14%)	2 (13.3%)	0.58
Duration of hospital stay, days, median (IQR)	10 (7.00-14.00)	12.00 (7.00-20.00)	0.38
Need of mechanical ventilation, n=32	5 (35.71%)	3 (20%)	0.34
First line medications, n=30			0.066
Pulse Methylprednisolone only	5 (41.67%)	1 (6.67%)	
IVIg only	2 (16.67%)	4 (26.67%)	
Methylprednisolone + IVIG	5 (41.67%)	6 (40.0%)	
Methylprednisolone +IVIG + Plasmapheresis	0 (0.0%)	4 (26.67%)	
Need of plasmapheresis	0 (0.00%)	4 (26.67%)	0.037
Interval between presentation and start of treatment, days	3.00 (1.50-7.50)	4.00 (1.00-8.00)	0.77
Outcome			0.037
Expired	0 (0.00%)	4 (26.67%)	
Survived	14 (100.00%)	11 (73.33%)	

\*Chi-square or Fisher's exact test (categorical variables), t-test (continuous variables), Wilcoxon rank-sum test (discrete variables) GCS = Glasgow coma scale, CSF = Cerebrospinal fluid, MRI = Magnetic resonance imaging, EEG = Electroencephalogram, HSV = Herpes simplex virus, IVIG = Intravenous immunoglobulin, MRS = Modified Rankin scale \*normal = ≤40, high = >40 \*\*low = <50, normal = 50-80, high = >80

**Table III: Univariable analysis for prognostic factors associated with poor outcome.**

Characteristics	Odds ratio (95%CI)	p-value*
<i>Age, years (mean ± SD)</i>		
<5 years	0.913 (0.765,1.088)	0.305
Ref		
5-10 years	0.112 (0.016,0.779)	0.027
>10 years	0.25 (0.027,2.32)	0.223
<i>GCS score on arrival, Median (IQR)</i>		
Seizures	0.972 (0.733,1.29)	0.843
Yes	1.091 (0.181,6.582)	0.924
No	Ref	
Behavioural changes		
Yes	0.5 (0.040,6.217)	0.59
No	Ref	
Speech disturbance		
Mutism	1.334 (0.274,6.497)	0.722
Dysarthria	-	-
No	Ref	
Psychiatric disturbances		
Yes	1.528 (0.314,7.437)	0.6
No	Ref	
Movement disorder		
Chorea	2.5 (0.370,16.889)	0.347
Dystonia	6 (0.423,85.248)	0.186
Tremors	2 (0.182,22.057)	0.571
Myoclonic jerks	-	-
No abnormal movements	Ref	
History of HSV encephalitis		
Yes	2 (0.161,24.871)	0.59
No	Ref	
CSF Protein*, n=32		
Normal	Ref	
High	8.667 (0.886,84.836)	0.064
CSF Glucose**, n=32		
Low	2.134 (0.329,13.814)	0.427
Normal	Ref	
High	0.229 (0.029,1.77)	0.158
CSF neuronal antibodies		
Positive	3.75 (0.794,17.72)	0.095
Negative	Ref	
Abnormal MRI findings		
Abnormal	1.112 (0.240,5.143)	0.893
Normal	Ref	
Abnormal EEG		
Abnormal	1.084 (0.132,8.947)	0.941
Normal	Ref	
Duration of hospital stay, days, median (IQR)	1.05 (0.948,1.163)	0.352
Need of mechanical ventilation, n=32		
Yes	0.45 (0.085,2.396)	0.349
No	Ref	
First line medications, n=30		
Pulse Methylprednisolone only	0.167 (0.015,1.938)	0.152
IVIg only	1.667 (0.211,13.224)	0.629
Pulse Methylprednisolone + IVIG	Ref	
Pulse Methylprednisolone +IVIG + plasmapheresis	-	-
Maintenance immunotherapy received		
Yes	1.112 (0.240,5.142)	0.893
No	Ref	
Interval between presentation and start of treatment, days, n=30	1.043 (0.853,1.276)	0.686
Interval from disease onset to admission, days		
≤14 days	Ref	
>14 days	1.2 (0.267,5.4)	0.812

\*Logistic regression. GCS = Glasgow coma scale, CSF = Cerebrospinal fluid, MRI = Magnetic resonance imaging, EEG = Electroencephalogram, IVIG = Intravenous immunoglobulin. \*normal = ≤40, high = >40. \*\*low = <50, normal = 50-80, high = >80.

One of the patients had acute retinal necrosis of her left eye seven years later and her PCR of ocular fluid was positive for HSV 1. She eventually developed left inferotemporal retinal scarring and is still on prophylactic oral acyclovir. Only 9% of patients had Type 2 (present only in CSF) oligoclonal bands. The remaining were positive for Type 4 (identical oligoclonal bands in CSF and serum). The baseline investigations including complete blood count and electrolytes were normal in all patients. Other autoimmune workups (ANA, anti-dsDNA) were negative and no tumour was identified. The most common EEG finding was diffuse delta theta slowing seen in 39.3% of patients, other abnormalities were focal slowing (15.1%) and epileptic discharges (21.2%). Extreme delta brush pattern was found in only one patient. The most common initial MRI abnormalities were T2 /Flair hyperintense signals in subcortical white matter and cortex seen in 15.1% and 12.1% of patients, respectively. Other MRI findings were hyperintense signals in hippocampus 2 (6%), brainstem 1 (3%), basal ganglia 1 (3%), leptomeningeal enhancement 1 (3%), and acute infarct in middle

cerebral artery (MCA) and posterior cerebral artery (PCA) territory 1 (3%).

First-line immunotherapy i.e. methylprednisolone pulse therapy, IVIG, plasmapheresis or combined therapy was given in 30 patients, while second-line immunotherapy (Rituximab) was used in 3 patients who did not respond to first-line therapy (Table I). Four (12.1%) patients died. One patient expired during the paediatric intensive care unit (PICU) stay, and the other 3 expired after a prolonged disease course due to pneumonia. CSF NMDA antibodies were positive in all patients who expired.

The prognosis for outcome was only done in 29 patients as 4 were lost to follow-up. Univariable analysis showed that the odds of having poor outcomes were 2.5 in patients with chorea. In addition, an elevated CSF protein had an OR of 8.6 and positive CSF antibodies had an OR of 3.7 for a poor outcome. Plasmapheresis was only needed in patients with poor outcome ( $p=0.037$ ; Tables II and III).

## DISCUSSION

This study evaluates the clinical course and outcome of autoimmune encephalitis in children admitted in the last 5 years. Reported data shows that AE can occur in any age group; however, almost 40% are younger than 18 years of age.<sup>2,15</sup> A third of the included patients were < 5 years of age. NMDAR encephalitis is the most prevalent variety of AE in the Asian population.<sup>10,16,17</sup> Fatema *et al.* report that 93% of patients with AE have NMDAR encephalitis.<sup>16</sup> Other studies from China and Sri Lanka, also report NMDAR encephalitis as the most prevalent subtype, followed by anti-LGI1, anti-CASPR2, anti-GABABR, and anti-AMPA encephalitis.<sup>10,17</sup> There are no case series from Pakistan regarding AE specifically in children. Haq AU *et al.* from Pakistan present the largest series of NMDAR encephalitis in 17 patients in which children < 12 years were 59%.<sup>12</sup> Another study by Shaikh *et al.* reported 8 patients from Pakistan with NMDAR encephalitis, amongst them 4 were children.<sup>13</sup> This study is unique as it reports the largest cohort of children with AE from Pakistan.

AE may be a clinical presentation reported as probable AE when antibodies are negative.<sup>4</sup> Wickramasinghe *et al.* reported 65 patients with AE, amongst them 44.6% were antibody positive.<sup>17</sup> Antibody positivity in this series was also close to this. The authors compared the clinical features of this cohort with the findings of a study by Wickramasinghe *et al.* who reported abnormal behaviour, seizures, and movement disorders as the most common manifestations, and did not find an associated tumour in any of the patients.<sup>17</sup> Seizures, behavioural symptoms, and movement disorder were the most common presenting symptoms not associated tumour. Haq *et al.* compared the movement disorders in NMDAR in children less than 12 years with those older than 12 years.<sup>12</sup> Catatonia and bradykinesia were more common in the older age > 12 years versus stereotypy, dystonia, chorea, and orofacial dyskinesia which were more common in children <12 years. In this study, chorea was the most common movement disorder followed by

dystonia, tremors, and myoclonic jerks. Catatonia was seen in only one patient who was 16 years.

The occurrence of anti-NMDAR encephalitis following HSV encephalitis is very well reported and can occur any time either during or even after the treatment has been completed.<sup>18-20</sup> Armangue *et al.* reported a 2-year infant girl who developed anti-NMDAR encephalitis a week after treatment for *Herpes simplex* encephalitis.<sup>19</sup> Two of the children developed AE whilst on acyclovir with sudden onset orofacial dyskinesias. Children may present with relapse after HSV treatment is completed in the form of choreoathetosis, behavioural or psychiatric changes.<sup>15,20</sup> Two patients of this series developed it as a relapse, one and four months later each with a negative HSV PCR in CSF. Oligoclonal bands are done as a part of diagnostic evaluation for AE.<sup>1</sup> Type 2 oligoclonal bands are reported to be positive in AE ranging from 13-60%.<sup>11,21</sup> In this study, Type 2 bands were positive in only 3 (9%) patients.

Previous data revealed nearly half of the patients with significant clinical improvement with first-line immunotherapy.<sup>2,15</sup> The efficacy of any particular type of individual first-line treatment is not yet established, but the use of early and combined therapy results in full recovery with no relapses.<sup>2,15</sup> Immunotherapy was used in 30 of the present patients. Six patients received only pulse methylprednisolone with a good outcome in 83.3%. Seven patients received IVIG as first-line therapy and 28.5% had a good outcome. Combined first-line therapies may be started in NMDAR encephalitis in severe cases but the quality of evidence is not strong.<sup>1</sup> In this study, 17 patients received combined therapy, out of these 5 (29.4%) improved to mRS score <2 at 3 months. Of the remaining 12 patients on combined therapy, 4 expired. Wickramasinghe *et al.* reported good outcome in 68.3% of their patients who received first-line therapy alone or in combination with second-line therapy.<sup>17</sup> Another study by Lee *et al.* showed that 62.2% of patients had an mRS score of <2 at one-year follow-up after first-line ± second-line immunotherapy.<sup>22</sup> In the present cohort, overall good outcome was seen in 48.2% of patients either with first-line therapy alone or in combination with second-line.

Previous studies have shown that around 35% of patients do not respond to first-line immunotherapy thus requiring second-line therapy.<sup>2,15</sup> In this study, second-line therapy (rituximab) was only given in three patients. Although AE has been known since the early part of the 20<sup>th</sup> century the understanding of this condition has only advanced in the past decade or so.<sup>2</sup> Rituximab being the first monoclonal antibody was developed for patients with cancer and has recently been added to the armamentarium of treatment for AE.<sup>1</sup> The Addition of plasmapheresis did not make any change in the outcome of the patients. This is contrary to the findings of a systematic review,<sup>23</sup> reporting that there were more chances of recovery when plasmapheresis was used with other modalities as first-line treatment, in this study's cohort all patients who required plasmapheresis had poor outcomes.

This study has some limitations. This was a retrospective single center study reviews the medical records of patients. In addition, due to the small number of patients, the authors could gain only limited information regarding the response to different types of immunotherapies and their association with outcome. The results were not significant. Follow-up was done for a limited period and the outcome might have changed if long-term follow-ups were done. Autoimmune encephalitis is a diagnostic challenge in Pakistan as only a few laboratories are performing this test and there is a turnaround time lag of 7-10 days. There are only six antibodies included in the antibody panel. Patients were not checked for anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody, which is a newly identified autoantibody. This could be the reason for the high numbers of probable AE in this cohort, although these cases clinically fulfilled the criteria of AE.

## CONCLUSION

Behavioural symptoms are the most common in children presenting with AE. Children with AE can have normal MRI, CSF analysis, and negative CSF antibodies. AE should be suspected earlier in children presenting with abnormal movements, and behavioural or psychiatric symptoms with or without altered consciousness.

### ETHICAL APPROVAL:

The study was approved by the Aga Khan University Hospital's Ethical Review Committee (2022-7685-22439).

### PATIENTS' CONSENT:

The need for informed consent was waived by the Aga Khan University Ethical Review Committee, due to the retrospective study design and anonymity of patient data.

### COMPETING INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

MR, KM: Design for this write-up, extracted the data, analysed, and interpreted the data and wrote the manuscript.

SI: Analysed and interpreted the data, wrote the manuscript, expert advice, and critically revised the manuscript.

All authors approved the final version of the manuscript to be published.

## REFERENCES

- Abboud H, Probasco JC, Irani S, Ances B, Benavides DR, Bradshaw M, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry* 2021; **92(7)**: 757-68. doi: 10.1136/jnnp-2020-325300.
- Brenton JN, Goodkin HP. Antibody-mediated autoimmune encephalitis in childhood. *Pediatr Neurol* 2016; **60**:13-23. doi: 10.1016/j.pediatrneurol.2016.04.004.
- Bien C, Bien C. Autoimmune encephalitis in children and adolescents. *Neurol Res* 2020; **2**:1-8. doi: 10.1186/s42466-019-0047-8.
- Cellucci T, Van Mater H, Graus F, Muscal E, Gallentine W, Klein-Gitelman MS, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm* 2020; **7(2)**:e663. doi: 10.1212/NXI.0000000000000663.
- Kahn I, Helman G, Vanderver A, Wells E. Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis: a survey of treatment progress and prospects from pediatric neurologists. *J Child Neurol* 2017; **32(2)**:243-45. doi: 10.1177/0883073816675557.
- Sai Y, Zhang X, Feng M, Tang J, Liao H, Tan L. Clinical diagnosis and treatment of pediatric anti-N-methyl-D-aspartate receptor encephalitis: A single center retrospective study. *Exp Ther Med* 2018; **16(2)**:1442-8. doi: 10.3892/etm.2018.6329
- Qiu X, Zhang H, Li D, Wang J, Jiang Z, Zhou Y, et al. Analysis of clinical characteristics and poor prognostic predictors in patients with an initial diagnosis of autoimmune encephalitis. *Front Immunol* 2019; **10**:1286. doi: 10.3389/fimmu.2019.01286.
- Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. *Lancet Neurol* 2013; **12(2)**:157-65. doi: 10.1016/S1474-4422(12)70310-1.
- Mo Y, Wang L, Zhu L, Li F, Yu G, Luo Y, et al. Analysis of risk factors for a poor prognosis in patients with anti-N-methyl-D-aspartate receptor encephalitis and construction of a prognostic composite score. *J Clin Neurol* 2020; **16(3)**:438-47. doi: 10.3988/jcn.2020.16.3.438.
- Qiao S, Wu H-K, Liu L-I, Zhang R-R, Wang M-I, Han T, et al. Characteristics and prognosis of autoimmune encephalitis in the East of China: A multi-center study. *Front Neurol* 2021; **12**:642078. doi: 10.3389/fneur.2021.642078.
- Hacohen Y, Wright S, Waters P, Agrawal S, Carr L, Cross H, et al. Paediatric autoimmune encephalopathies: Clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *J Neurol Neurosurg Psychiatry* 2013; **84(7)**:748-55. doi: 10.1136/jnnp-2012-303807.
- Haq AU, Nabi D, Alam M, Ullah SA, Haq MA, Ullah S. The spectrum of movement disorders in anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis both in children and adults: An experience from a single tertiary care center. *Cureus* 2021; **13(12)**:e20376. doi: 10.7759/cureus.20376.
- Sheikh S, Ahmad A, Ahmed TA. Anti NMDA receptor antibody encephalitis in Pakistan: Clinicopathological features and treatment outcomes. *JPMA* 2019; **69(12)**: 1910-14. doi: 10.5455/JPMA.300185.
- Nosadini M, Thomas T, Eyre M, Anlar B, Armangué T, Benseler SM, et al. International consensus recommendations for the treatment of pediatric NMDAR antibody encephalitis. *Neurol Neuroimmunol Neuroinflamm* 2021; **8(5)**:e1052. doi: 10.1212/NXI.0000000000001052.

15. Gastaldi M, Thouin A, Vincent A. Antibody-mediated autoimmune encephalopathies and immunotherapies. *Neurother* 2016; **13(1)**:147-62. doi: 10.1007/s13311-015-0410-6.
16. Fatema K, Rahman MM. Pediatric Autoimmune encephalitis: Experience from a Tertiary Care Hospital in Bangladesh. *J Int Child Neurol Assoc* 2021; **1(1)**. doi: 10.17724/jicna.2021.200
17. Wickramasinghe N, Dasanayake D, Malavige N, de Silva R, Chang T. Autoimmune encephalitis in a South Asian population. *BMC Neurol* 2021; **21(1)**:1-8. doi: 10.1186/s12883-021-02232-6.
18. DeSena A, Graves D, Warnack W, Greenberg BM. Herpes simplex encephalitis as a potential cause of anti-N-methyl-D-aspartate receptor antibody encephalitis: Report of 2 cases. *JAMA Neurol* 2014; **71(3)**:344-46. doi: 10.1001/jamaneurol.2013.4580.
19. Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013; **162(4)**:850-56. doi: 10.1016/j.jpeds.2012.10.011.
20. Nosadini M, Mohammad SS, Corazza F, Ruga EM, Kothur K, Perilongo G, et al. Herpes simplex virus-induced anti-N-methyl-d-aspartate receptor encephalitis: A systematic literature review with analysis of 43 cases. *Dev Med Child Neurol* 2017; **59(8)**:796-805. doi: 10.1111/dmcn.13448.
21. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; **10(1)**:63-74. doi: 10.1016/S1474-4422(10)70253-2.
22. Lee S, Kim HD, Lee JS, Kang HC, Kim SH. Clinical features and treatment outcomes of seronegative pediatric autoimmune encephalitis. *J Clin Neurol* 2021; **17(2)**:300-6. doi: 10.3988/jcn.2021.17.2.300.
23. Suppiej A, Nosadini M, Zuliani L, Pelizza MF, Toldo I, Bertossi C, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. *Brain Dev* 2016; **38(7)**: 613-22. doi: 10.1016/j.braindev.2016.01.009.

