Section: Pediatric Medicine

Original Research Article

STUDY OF CLINICOEPIDEMIOLOGICAL PROFILE, IMAGING & OUTCOME OF CHILDREN ADMITTED WITH AUTOIMMUNE ENCEPHALITIS & PREDICTION OF AUTOIMMUNE RELATED EPILEPSY AMONG THEM – A TERTIARY CENTER STUDY IN KOLKATA

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Abstract

Background: Encephalopathy in children and adolescents is associated with a high rate of morbidity and mortality and poses difficult diagnostic and therapeutic challenges. The differential diagnoses are diverse, including infectious, para-infectious, metabolic, genetic, traumatic, malignant and toxic disorders. **Aims:** The aim to study the clinico-epidemiological profile, Imaging (MRI Brain & EEG) & outcome of children admitted with autoimmune encephalitis. **Materials & Methods:** The present study was an Observational prospective study. This Study was conducted from Nov 2022 to April 2024 at Calcutta National Medical College & Hospital. Total 17 patients were included in this study. **Results:** In our study, 13 (76.5%) patients had Cells (Leucocytes) >5/mm3, 5 (29.4%) patients had High CSF protein >50 mg/dl and 4 (23.5%) patients had Oligoconal bands CSF findings. The value of z is 3.087. The value of p is .002. The result is significant at $p < .05$. **Conclusion:** Autoimmune Encephalitis is a potentially fatal disease with significant morbidity & mortality with but with good outcome to immunotherapy. Identifying patients with an underlying autoimmune origin is critical because these patients' condition may remain refractory to conventional antiseizure medications but may respond to immunotherapy. In our study we found abnormal MRI findings & response to 2nd line immunotherapy in AE to be statistically significant. (p value<0.05) We also found that APE & RITE scores can predict diagnosis & response to immunotherapy respectively in patients with ARE with high sensitivity. However we recommend people to do further studies in this field with more sample size.

INTRODUCTION

Children's and teens' encephalopathy presents challenging diagnostic and treatment issues and is linked to a high rate of morbidity and mortality.[1] The differential diagnoses are diverse, including infectious, para-infectious, metabolic, genetic, traumatic, malignant and toxic disorders.[2] The clinical features of these disorders overlap and, in many cases, the cause will not be apparent from the history and examination at presentation. Clinical observation, investigation and treatment often need to be carried out simultaneously.[3]

AUTOIMMUNE ENCEPHALITIS: Antibody-mediated encephalopathies are disorders in which patients exhibit neurological symptoms that are typically linked to antibodies in serum and/or cerebrospinal fluid (CSF) that target synaptic receptors and neuronal cell surface proteins involved in neuronal excitability, plasticity, or synaptic transmission.[4,5] It includes a growing set of clinical disorders that primarily affect children and young adults, but can occur at any age (less than a year to adulthood).Although the majority of these conditions are serious and potentially lethal, patients usually have positive results on immunotherapy.[6]

AUTOIMMUNE RELATED EPILEPSY (ARE): Autoimmunity, or a potential autoimmune etiology, has been implicated in a considerable percentage of cryptogenic epilepsies (15–20%).[6] Determining an autoimmune etiology affects seizure outcomes and management (immunotherapeutic in addition to traditional anticonvulsants).[7] While specific neural Ab results are required, an early clinical diagnosis may be possible with a grading system based on clinical characteristics and the initial neurologic assessment of patients with epilepsy. Prompt immunotherapy commencement is justified by the prediction of a good immunotherapeutic response, which may decrease the severity of neurologic impairment.[8] The aim to study the clinico-epidemiological profile, Imaging (MRI Brain & EEG) & outcome of children admitted with autoimmune encephalitis.

MATERIALS AND METHODS

Study Area: Calcutta National Medical College & Hospital
Study Design: Observational prospective study
Study Period: Nov 2022 to April 2024
Inclusion Criteria
Children admitted in Pediatric Ward & PICU between age 1 month to 12 yrs included with Probable AE (antibody negative) & Definite AE (antibody positive) in our study.
For autoimmune related epilepsy- both 'acute symptomatic seizures secondary to autoimmune encephalitis' & 'Autoimmune associated epilepsy' were included in our study. [9]
Children whose parents gave Consent for the same.
Exclusion Criteria
Children with possible other causes of encephalitis/encephalopathy/seizures like possible infective, metabolic, genetic, traumatic, toxic causes or demyelinating disorders etc.
Parents/ Guardians didn't give consent to be included in our study.
Sample Size: A total of 17 samples have been included in this study.
Statistical Analysis
For statistical analysis, data were initially entered into a Microsoft Excel spreadsheet and then analyzed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Numerical variables were summarized using means and standard deviations, while categorical variables were described with counts and percentages. Two-sample t-tests, which compare the means of independent or unpaired samples, were used to assess differences between groups. Paired t-tests, which account for the correlation between paired observations, offer greater power than unpaired tests. Chi-square tests (χ^2 tests) were employed to evaluate hypotheses where the sampling distribution of the test statistic follows a chi-squared distribution under the null hypothesis; Pearson's chi-squared test is often referred to simply as the chi-squared test. For comparisons of unpaired proportions, either the chi-square test or Fisher's exact test was used, depending on the context. To perform t-tests, the relevant formulae for test statistics, which either exactly follow or closely approximate a t-distribution under the null hypothesis, were applied, with specific degrees of freedom indicated for each test. P-values were determined from Student's t-distribution tables. A p-value ≤ 0.05 was considered statistically significant, leading to the rejection of the null hypothesis in favour of the alternative hypothesis.

RESULTS

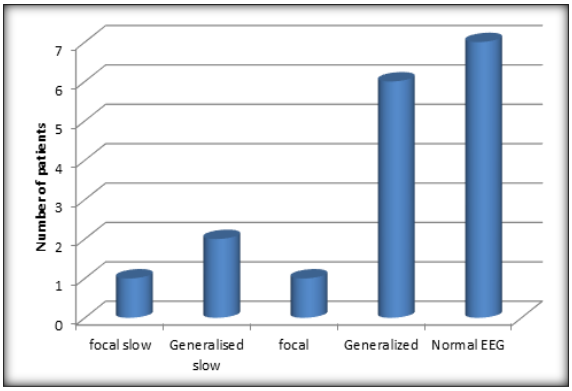

Figure 1: Distribution of EEG findings

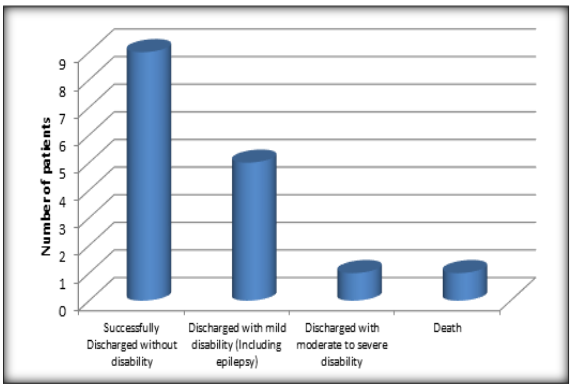

Figure 2: Distribution of Outcome of patients

In our study, 13 (76.5%) patients had Cells (Leucocytes) >5/mm3, 5 (29.4%) patients had High CSF protein >50 mg/dl and 4 (23.5%) patients had Oligoconal bands CSF findings. The value of z is 3.087. The value of p is .002. The result is significant at $p < .05$. In our study, 7 (41.2%) patients had Only steroid, 5 (29.4%) patients had Steroid+ IVIG, 5 (29.4%) patients had Steroid + IVIG + Rituximab and 2 (11.8%) patients had Steroid + IVIG + Rituximab+ Cyclophosphamide. The value of z is 1.9078. The value of p is .05614. The result is not significant at $p < .05$. In Seropositive ARE, 5 patients had APE score ≥4 and 1 patient had APE score <4. In Seronegative ARE, 7 patients had APE score ≥4 and 1 patient had APE score <4. Association of APE with Seropositive ARE was statistically significant (p=0.001) and APE with Seronegative ARE was statistically significant (p<0.001). In Seropositive ARE, 6 patients had RITE

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score ≥7. In Seronegative ARE, 6 patients had RITE score ≥7 and 2 patients had RITE score <7. Association of RITE score with Seropositive ARE was statistically significant (p=0.001). In Seropositive, 5 patients had altered level of consciousness, 6 patients had Seizure, 4 patients had Behavioral Abnormality, 3 patients had Sleep abnormality, 3 patients had Speech problem, and 2 patients had Movement Disorder. In Seronegative, 8 patients had altered level of consciousness, 5 patients had Seizure, 6 patients had Behavioral Abnormality, 5 patients had Sleep abnormality, 6 patients had Speech problem, and 4 patients had Movement Disorder. Association of Clinical symptoms with group was not statistically significant (p= 0.9375)

RITE score with Seronegative ARE was statistically significant (p=0.001. In our study, 1 (5.9%) patient had focal slow, 2 (11.7%) patients had Generalised slow of Background rhythm slow. 1 (5.9%) patient had focal, 6 (35.2%) patients had Generalized in Epileptic discharges and 7 (41.2%) patients had Normal EEG. The value of z is 2.4258. The value of p is .0151. The result is significant at p < .05. In our study, 9 (52.9%) patients had Successfully Discharged without disability, 5 (29.4%) patients had Discharged with mild disability (Including epilepsy), 1 (5.9%) patient had Discharged with moderate to severe disability and 1 (5.9%) patient had Death in Outcome of patients. The value of z is 3.0511. The value of p is .00228. The result is significant at p < .05.

Table 1: Distribution of CSF Findings and MRI Brain findings

	Parameter	No (percentage) (n=17)	p-value
CSF findings	Cells (Leucocytes) >5/mm3	13 (76.5%)	.002
	High CSF protein >50 mg/dl	5 (29.4%)	
	Oligoconal bands	4 (23.5%)	
MRI Brain findings	Temporal/hippocampal involvement	2 (11.7%)	.00262
	Cortical lesion	2 (11.7%)	
	Basal ganglia/ Thalamus involvement	1 (5.9%)	
	Overlapping pictures/other nonspecific findings	3 (17.6%)	
	Normal MRI	9 (52.9%)	

Table 2: Distribution of Immunotherapy Requirement

Immunotherapy required	No (Percentage)	p-value
Only steroid	7 (41.2%)	.05614
Steroid+ IVIG	5 (29.4%)	
Steroid + IVIG + Rituximab	5 (29.4%)	
Steroid + IVIG + Rituximab+ Cyclophosphamide	2 (11.8%)	

Table 3: Association between Between APE score with Seropositive & Seronegative AE

		Seropositive ARE (n=6)	Seronegative ARE (n=8)	p value
APE score	APE score ≥4	5	7	0.001
	APE score <4	1	1	<0.001
RITE score	RITE score ≥7	6	6	0.001
	RITE score <7	0	2	0.001

Table 4: Distribution of Outcome of patients

Outcome of patients	mRs score (modified Rankin scale)	No (Percentage)	p-value
Successfully Discharged without disability	0	9 (52.9%)	.00228
Discharged with mild disability (Including epilepsy)	1-2	5 (29.4%)	
Discharged with moderate to severe disability	3-5	1 (5.9%)	
Death	6	1 (5.9%)	

Table 5: Distribution of Clinical symptoms

Clinical symptoms	Seropositive (n=7)	Seronegative (n=10)	Total
Altered level of consciousness	5	8	13
Seizure	6	5	11
Behavioral Abnormality	4	6	10
Sleep abnormality	3	5	8
Speech problem	3	6	9
Movement Disorder	2	4	6

DISCUSSION

In our study, 13 (76.5%) patients had Cells (Leucocytes) >5/mm3 which was statistically significant .002 Wegener-Panzer A et al,[10] (2020) found that CSF pleocytosis was common (9/10, median 80 white cell count/μL, range: 21–256). Imaging showed cortical and deep gray matter involvement in all in addition to juxtacortical signal alterations in 6/10 children. No involvement of other white matter structures or contrast enhancement was noted. MOG abs were detected in all children (median titer 1:640; range: 1:320–1:10,540). Nine children had a favorable outcome at discharge

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(modified Rankin scale of < 2). Also Dubey D et al,[11] (2017) found that Serum and cerebrospinal fluid (CSF) from 1,736 patients were sent to the Mayo Clinic Neuroimmunology Laboratory for neural autoantibody evaluation. Three hundred eighty-seven of these patients met the diagnostic criteria for epilepsy. Central nervous system (CNS)-specific antibodies were detected in 44 patients. Certain clinical features such as new-onset epilepsy, autonomic dysfunction, viral prodrome, faciobrachial dystonic seizures/oral dyskinesia, inflammatory CSF profile, and mesial temporal magnetic resonance imaging (MRI) abnormalities had a significant association with positive antibody results. A significantly higher proportion of antibody-positive patients had an APE score ≥4 (97.7% vs. 21.6%, p < 0.01).

In our study 9 (52.9%) patients had Normal MRI of MRI Brain findings. This was statistically significant .00262. Dubey D et al,[11] (2017) found that in 44 patients. Certain clinical features such as new-onset epilepsy, autonomic dysfunction, viral prodrome, faciobrachial dystonic seizures/oral dyskinesia, inflammatory CSF profile, and mesial temporal magnetic resonance imaging (MRI) abnormalities had a significant association with positive antibody results. A significantly higher proportion of antibody-positive patients had an APE score ≥4 (97.7% vs. 21.6%, p < 0.01). Sensitivity and specificity of an APE score ≥4 to predict presence of specific neural auto-antibody were 97.7% and 77.9%, respectively.

In our study 6 (35.2%) patients had Generalized in Epileptic discharges and 7 (41.2%) patients had Normal EEG. This was statistically significant .0151

In our study, 7 (41.2%) patients had only steroid which was statistically significant .05614.

In our study, 9 (52.9%) patients had Successfully Discharged without disability which was statistically significant .00228.

In our study 7 patients had APE score ≥4 in Seronegative ARE compare to 5 patients had APE score ≥4 in Seropositive ARE which was statistically significant (p<0.001). Dubey D et al,[11] (2017) found that A significantly higher proportion of antibody-positive patients had an APE score ≥4 (97.7% vs. 21.6%, p < 0.01). Sensitivity and specificity of an APE score ≥4 to predict presence of specific neural auto-antibody were 97.7% and 77.9%, respectively. In the subset of patients who received immunotherapy (77), autonomic dysfunction, faciobrachial dystonic seizures/oral dyskinesia, early initiation of immunotherapy, and presence of antibodies targeting plasma membrane proteins (cell-surface antigens) were associated with favorable seizure outcome.

In our study 6 patients had RITE score ≥7 in both group which was statistically significant (p<0.001). Dubey D et al,[11] (2017) found that Sensitivity and specificity of an APE score ≥4 to predict presence of specific neural auto-antibody were 97.7% and 77.9%, respectively. In the subset of patients who received immunotherapy (77), autonomic dysfunction, faciobrachial dystonic seizures/oral dyskinesia, early initiation of immunotherapy, and presence of antibodies targeting plasma membrane proteins (cell-surface antigens) were associated with favorable seizure outcome. Sensitivity and specificity of a RITE score ≥7 to predict favorable seizure outcome were 87.5% and 83.8%, respectively.

CONCLUSION

Autoimmune Encephalitis is a potentially fatal disease with significant morbidity & mortality with but with good outcome to immunotherapy. Identifying patients with an underlying autoimmune origin is critical because these patients' condition may remain refractory to conventional antiseizure medications but may respond to immunotherapy.[7] In our study we found abnormal MRI findings & response to 2nd line immunotherapy in AE to be statistically significant. (p value<0.05) We also found that APE & RITE scores can predict diagnosis & response to immunotherapy respectively in patients with ARE with high sensitivity. However we recommend people to do further studies in this field with more sample size.

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