ORIGINAL ARTICLE

Clinical Spectrum of Autoimmune Encephalitis in Children at Tertiary Care Hospital

SAMEEN QURESHI, AMBER SHABIR, TIPU SULTAN, JAVERIA RAZA ALVI

Pak Pediatr J 2024; **48(3):** 246-52

Correspondence to:

Dr. Sameen Qureshi,
Department of Pediatric Neurology, University of Child Health Sciences, The Children's Hospital, Lahore

E-mail: sameenq@hotmail.com

Received 27th November 2023;
Accepted for publication
2nd September 2024

ABSTRACT

Objective: To study the clinical spectrum and functional outcome of autoimmune encephalitis in children.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Pediatric Neurology, University of Child Health Sciences, The Children's Hospital, Lahore. (a tertiary care hospital) after getting ethical approval from the Institutional Review Board via letter no.661.

Material and Methods: It was a cross-sectional study. We retrospectively analysed the records of patients diagnosed with autoimmune encephalitis from May 2022 to April 2023. The attendants of the study participants who fulfilled the inclusion criteria filled out a validated questionnaire. We documented the data on demographic information, clinical features, laboratory findings, radiological investigations, treatment given and their outcomes. The collected data were analysed using SPSS v26, whereas frequencies, percentages, ANOVA and post hoc tests were applied.

Results: Most of the study participants were male and presented with encephalopathy. Cerebrospinal fluid NMDA receptor antibodies were negative in two-thirds of the patients, while one-third tested positive. Regarding the clinical spectrum of autoimmune encephalitis, the most prevalent symptoms included disorganized speech, agitation, primary febrile illness, anxiety, paranoia, social withdrawal, insomnia, severe cognitive dysfunction, and an increased frequency of seizures. ANOVA for between treatment analysis showed significant values for intravenous immunoglobulins (IVIG) and Rituximab ($p \leq 0.05$) whereas for methylprednisolone it was non-significant ($p \geq 0.05$). Post hoc values showed a significant difference ($p \leq 0.05$) between the post treatment scores of methylprednisolone and IVIG or Rituximab.

Conclusion: Autoimmune encephalitis has shown a diverse range of symptoms in our study participants, with IVIG and Rituximab as the better treatment option than merely steroids.

Key Words: *Autoimmune encephalitis, Clinical spectrum*, *Intravenous immunoglobulins, Rituximab*

INTRODUCTION

Autoimmune encephalitis (AE) is a group of disorders characterized by symptoms of limbic and extra-limbic dysfunction associated with antibodies against synaptic antigens and proteins localized on the neuronal cell surface.[1,2] In annual incidents of 2.3/100000 in Northern Europe, 40% of cases are infectious, 40% are of unknown cause, and 20% are the immune-mediated largest group of anti-NMDA receptor encephalitis (4%).[3,4]

The clinical spectrum of AE is diverse, ranging from mild cognitive and psychiatric symptoms to severe encephalopathy, seizures, and even coma.[5] The symptoms are typically sub-acute and progress over weeks to months.[6] Some patients may have a prodromal phase characterized by flu-like symptoms, fever, headache, or seizures.[7] The clinical presentation varies depending on the type of autoantibodies involved, the age and sex of the patient, and the underlying etiology of the disease.[8]

We can broadly classify AE into classical and non-classical categories.[9] Classical AE is associated with well-characterized autoantibodies, such as anti-NMDAR, anti-leucine-rich glioma inactivated protein 1 (LGI1), anti-contactin-associated protein-like 2 (CASPR2), anti-GABA (B) receptor, anti-amphiphysin, anti-mGluR5, and anti-DPPX.[10] These autoantibodies target specific neuronal antigens associated with characteristic clinical features.[11] For example, anti-NMDAR encephalitis typically presents with psychiatric symptoms, seizures, and movement disorders, whereas anti-LGI1 encephalitis is associated with limbic encephalitis, hyponatremia, and seizures.[12] Non-classical AE refers to a group of patients with clinical features of AE but no known autoantibodies.[13]

The diagnosis of AE is challenging, and a high index of suspicion is required to recognize this condition. It requires a multidisciplinary approach, including neurologists, psychiatrists, immunologists, and radiologists.[14] The diagnosis is based on a combination of clinical features, neuroimaging, electroencephalography (EEG), cerebrospinal fluid (CSF) analysis, and the presence of specific autoantibodies.[15]

Children present with a polysymptomatic presentation, including behavioural changes, psychosis, sleep disturbances, mutism, seizures, movement disorders, memory impairment, as well as other neurocognitive deficits.[16] Since the patients respond well to immunosuppressive treatment.[17,18] It is very important to recognize this disorder. Antibodies provide information on prognosis and are used for disease classification. The patients with definite autoimmune encephalitis had MRI abnormalities within limbic structures, most notably the anteromedial temporal lobes (56%). Only individuals with the suspected disease had nontemporal lobe cortical lesions.[19] The best-studied disorder is anti-NMDA receptor encephalitis,[19,20] in which the titer-dependent decrease of receptors by a capping, cross-linking, and internalization of the receptors.

In anti-NMDA receptor encephalitis, there is local production of autoantibodies in the brain and meninges, and 13% of patients develop partial forms of the syndrome characterized by predominant psychiatric disturbance, refractory seizures, status epilepticus, or movement disorders. Early first-line immunotherapies, including corticosteroids and plasma exchange, improve outcomes, with emerging evidence showing that second-line immunotherapies (especially rituximab) reduce relapse rates.[21] Early recognition, prompt diagnosis, and timely intervention are the key features of patients with NMDR-positive antibodies. So, this study aimed to characterize the clinical spectrum, treatment responses, and outcomes of pediatric patients with autoimmune encephalitis at a tertiary care hospital. By conducting a cross-sectional analysis, we sought to determine the distribution of cerebrospinal fluid NMDA receptor antibodies and to compare post-treatment outcomes. Specifically, we aimed to identify the most prevalent symptoms and evaluate the efficacy of different treatment options, including Methylprednisolone, intravenous immunoglobulins (IVIG), and rituximab. This study was designed to provide insights into the optimal management strategies, whether an expensive treatment for pediatric autoimmune encephalitis, with the ultimate goal of early diagnosis, improving patient care and treatment efficacy and preventing persistent deficits in our population.

METHOD AND MATERIALS

Study design*:* This cross-sectional study was conducted at the Department of Pediatric Neurology, University of Child Health Sciences, The Children's Hospital, Lahore (a tertiary care hospital). The retrospective data was collected from May 2022 to April 2023.

This study was ethically approved by the Institutional Review Board of the Children's Hospital, Lahore via letter no.661. A validated questionnaire was used for the data collection, which attendants filled out after obtaining informed consent. A non-probability convenience sampling technique was used to select study participants.

Study participants and inclusion criteria: The sample size of this study was 23, which was determined using the following formula:

$$Sample\ size = \frac{Z_{1-a/2^2}\,P(1-P)}{d^2}$$

This study included children aged from 6 months to 18 years but diagnosed with Auto-immune encephalitis (4 stages). These patients were treated for symptoms of viral encephalitis but had no clinical improvement. Moreover, they had prodromal symptoms (Fever, headache, nausea, vomiting and upper gastrointestinal symptoms). In this study, patients with psychiatric and behavioural symptoms, memory deficits and abnormal movements were also included. They had positive anti-NMDA antibodies and an Electroencephalogram showing an 'extreme delta brush pattern'. The patients who had neurometabolic disorders, central nervous disorders and other movement disorders with genetic aetiology of the specific age were excluded from the study.

Study procedure: This study was cross-sectional. Researchers obtained formal informed consent from the patient's attendants, who met the inclusion criteria. Data were collected using a validated questionnaire, which included demographic and biographic information of the study participants. Researchers recorded clinical, laboratory, and radiological findings. The presence of the Anti-NMDA receptor antibody was confirmed through testing. Treatment was administered to the patients, and the responses to the treatment were recorded.

Statistical analysis: The data was analyzed using SPSS v26. The qualitative data was reported using percentages and frequency. Researchers applied the Shapiro-Wilk test to evaluate the normality of the data. ANOVA was used for between-group analyses, whereas the post hoc test was used for multiple comparisons. The significance level for this study was set at $\alpha = 0.05$.

RESULTS

Of the total 23 study participants, 13 were male and 10 female, with a mean age of 7.3 years. Consanguinity was present in 30.4% of the patients, and febrile illness was present in 95.7%. The major characteristics found among all participants were social withdrawal and sleep disturbances. The common symptoms among participants reported were anxiety (95.7%), paranoia (91.3%), agitation (91.3%), change in speech (82.6%), disorganized thinking (95.7%), catatonia (91.3%), insomnia (95.7%), and severe cognitive dysfunction (91.3%). An increase in seizure frequency (69.6%) was also reported among patients, along with recovery and relapse (82.6%). These patients had prolonged deficits (65.2%) and executive dysfunction (87.0%). Disinhibition (95.7%), hypertonia (69.6%) and encephalopathy (60.9%) were detected in the majority of patients. Results revealed intractable seizures and moderate memory dysfunction in 65.2 and 60.9% of the patients, respectively. An overwhelming majority (87%) of patients had executive dysfunctions. The persistence of hallucinations (30.4%), delusions (4.3%), cancer (0%), mania (8.7%), tachycardia (13.0%), and impulsivity (21.7%) were the least among participants (table 1).

TABLE 1 Characteristics of the patients with AE (n=23)

Variables		Frequency	Percentage
Gender	Male	13	56.5
	Female	10	43.5
Consanguinity	Yes	7	30.4
	No	16	69.6
Febrile illness	Yes	22	95.7
	No	1	4.3
Anxiety	Yes	22	95.7
	No	1	4.3
Paranoia	Yes	21	91.3

	No	2	8.7
Hallucination	Yes	7	30.4
	No	16	69.6
Delusion	Yes	1	4.3
	No	22	95.7
Social withdrawal	Yes	23	100.0
	No	0	0.0
Mania	Yes	2	8.7
	No	21	91.3
Agitation	Yes	21	91.3
	No	2	8.7
Change in speech	Yes	19	82.6
	No	4	17.4
Disorganized thinking	Yes	22	95.7
	No	1	4.3
Catatonia	Yes	21	91.3
	No	2	8.7
Hyperthermia	Yes	5	21.7
	No	18	78.3
Insomnia	Yes	22	95.7
	No	1	4.3
BP fluctuation	Yes	4	17.4
	No	19	82.6
Tachycardia	Yes	3	13.0
	No	20	87.0
Increase seizure frequency	Yes	16	69.6
	No	7	30.4
Impulsivity	Yes	5	21.7
	No	18	78.3
Disinhibition	Yes	22	95.7
	No	1	4.3
Sleep disturbance	Yes	23	100.0
	No	0	0.0
Ataxia	Yes	1	4.3
	No	22	95.7
Encephalopathy	Yes	14	60.9
	No	9	39.1
Executive dysfunction	Yes	20	87.0
	No	3	13.0

Laboratory investigations showed that 87.0 % of patients had normal CSF. NMDA receptor antibodies were detected in 34.8% of patients, and 60.9% showed abnormal EEG findings. The CASE score showed that the treatment improved 95.7% of the patients, as shown in table 2.

TABLE 2: Laboratory investigation of the patients and improvement in treatment response (CASE score)

CSF	Normal	20	87.0
	Deranged	3	13.0
Csf NMDA Antibodies	Negative	15	65.2
	Positive	8	34.8
MRI findings	Normal	19	82.6
	Changes in MRI	4	17.4
EEG	Normal	9	39.1
	Changes in EEG	14	60.9
Cancer screening	Yes	0	0.0
	No	23	100.0
Case Score	Improved	22	95.7
	Not improved	1	4.3

Patients' mean age (in years) was 7.32 ± 3.71, whereas the mean of seizures was 2.52 ± 0.73, showing controlled to intractable seizures. The language problems were reported to be mild to moderate (2.21 ± 0.51), with hypertonia and drowsy consciousness. The psychiatric problems, gait instability and ataxia, memory dysfunction, dystonia and weakness were identified as mild to moderate in intensity. These symptoms were documented during the First and second week of disease (table 3).

TABLE 3: Mean and standard deviations of age, symptoms of diseases and onset of symptoms

	Sum	Mean	Std. Deviation
Age	166.50	7.23	3.71
Seizures	58.00	2.52	0.73
Language problem	51.00	2.21	0.51
Tone	48.00	2.08	0.41
Consciousness	47.00	2.04	0.76
Psychiatric symptoms	39.00	1.69	0.55
Gait instability and ataxia	37.00	1.60	0.49

Memory Dysfunction	37.00	1.60	0.49
Dystonia	31.00	1.34	0.57
Weakness	29.00	1.26	0.44
Onset of symptoms	39.00	1.69	0.55

Table 4 shows the treatment given to the patients. As the first line of treatment, Methylprednisolone was given to patients, and it showed a mean ± S.D of 1.78 ± 0.90. This treatment had poor to partial response in the patients. The patients not treated with the first line of treatment were given IVIG and rituximab; These values showed that IVIG had a better response than rituximab. Overall, the pre-treatment scores were improved from 10.52 to 3.00, as shown in table 4.

TABLE 4: Treatment given to patients (n=23)

	Sum	Mean	Std. Deviation
Methylprednisolone	41.00	1.78	0.90
IVIG	84.00	2.65	0.93
Rituximab	72.00	2.13	1.28
Pre-treatment score	242.00	10.52	2.88
Post-treatment score	69.00	3.00	2.31

ANOVA was used for between-group analyses, which showed statistically significant values for IVIG and rituximab ($p<0.05$). The F value of IVIG shows a better response on AE, as shown in table 5.

TABLE 5: ANOVA for between group analyses

Treatment given	Sum of Squares	Df	F	Sig.
Methylprednisolone	4.371	2	3.051	.074
	12.179	17		
IVIG	11.250	2	191.250	.000
	.500	17		
Rituximab	30.200	2	85.567	.000
	3.000	17		

Table 6 compares different treatments using the post hoc test. The results indicated a statistically significant difference ($p<0.05$) between the treatment of methylprednisolone, IVIG and rituximab, but a statistically non-significant difference ($p >0.05$) IVIG and rituximab.

TABLE 6: Post hoc test for different treatments

		Mean Difference (I-J)	Std. Error	Sig.
Methylprednisolone	IVIG	0.42857	.63982	1.000
	Rituximab	1.17857	.47986	.075
IVIG	Methylprednisolone	2.50000*	.12964	.000
	Rituximab	2.50000*	.14852	.080
Rituximab	Methylprednisolone	3.00000*	.31755	.000
	IVIG	-0.50000	.36380	.562

DISCUSSION

Autoimmune encephalitis (AE) exhibits a broad clinical spectrum globally, with variations influenced by geographical and demographic factors. This study aimed to characterize the clinical presentation of AE in a pediatric population from our region, contributing to the growing body of knowledge on this condition.

Our findings indicate that disorganized speech was the most prominent feature observed, contrary to previous studies[16,17] that reported a moderate prevalence of 58% for this symptom. This elevated prevalence in our cross-sectional study could be attributed to genetic predispositions unique to our population.

Agitation emerged as a highly prevalent symptom,

consistent with earlier research on AE.[17,18] This is likely due to disturbances in brain function, particularly involving areas responsible for emotional regulation. Similarly, primary febrile illness was observed in 95% of our subjects, significantly higher than reported in other studies [(17)]. This may be linked to hypothalamic dysfunction, as the hypothalamus plays a crucial role in fever regulation.[5]

Additionally, febrile illnesses were frequently associated with agitation and dystonias, underscoring the interconnectedness of these symptoms in AE. Encephalopathy, characterized by high prevalence rates of sleep disturbances, was another major finding. However, our study reported lower rates of encephalopathy compared to previous research.[6,7]

Interestingly, NMDA receptor antibodies were detected in only one-third of the cerebrospinal fluid samples.[19,20] This suggests that while NMDA receptor antibodies are a key diagnostic marker for AE, the broader clinical spectrum is crucial for diagnosis. This finding challenges the traditional reliance on antibody presence alone for AE diagnosis.

Our study noted several discrepancies with previous research. For instance, mania was not prevalent among our subjects, contrasting with some earlier studies[21-23] which reported psychiatric illness as the prominent feature in AE. Social withdrawal, however, was consistent with previous findings, indicating a strong association with AE. Hyperthermia was not the feature of AE in our study, which differs from earlier reports.[16,17] The discrepancies documented may be due to change in demographics and ethnicity of our population.

After appropriate management, i.e., administration of IVIG and rituximab, which proved to be an expensive treatment, most patients showed significant recovery. However, executive dysfunction persisted in some, with prolonged deficits observed during follow-up. This contrasts with an earlier study that reported fewer long-term deficits, possibly due to differences in patient presentation and post-discharge care.[18]

Comprehensive investigations, including cancer screening, neuroimaging, and electro-encephalography, were performed to identify comorbidities, yielding predominantly negative results. More than half of the patients responded well to intravenous steroids, corroborating evidence-based medicine which supports the efficacy of steroids in treating AE as an autoimmune disorder.[19] Patients unresponsive to steroids showed improvement with intravenous immunoglobulins (IVIG) and rituximab, aligning with previous research findings.[24,25]

Memory dysfunction and psychiatric symptoms were of moderate severity in our cohort, similar to the findings of other studies.[16,20] These observations highlight the varied neuropsychiatric manifestations of AE and the necessity for tailored therapeutic approaches.

Despite the significant insights provided by our study, limitations such as a small sample size necessitate caution in generalizing the findings. Future research should involve larger cohorts to validate these results. Additionally, exploring alternative treatment modalities based on evidence-based medicine could further enhance patient outcomes.

In conclusion, our study underscores the diverse clinical spectrum of AE in pediatric populations, emphasizing the importance of comprehensive clinical assessment in diagnosis and management. Continued research in this area will enhance our understanding and improve care strategies for patients with AE.

CONCLUSION

In conclusion, our study found that most participants with autoimmune encephalitis were male and presented with encephalopathy, with two-thirds testing negative for cerebrospinal fluid NMDA receptor antibodies. The clinical spectrum was diverse, with prevalent symptoms including disorganized speech, agitation, primary febrile illness, anxiety, paranoia, social withdrawal, insomnia, severe cognitive dysfunction, and increased seizure frequency. Treatment analysis indicated that intravenous immunoglobulins (IVIG) and Rituximab were significantly more effective than Methylprednisolone, which did not improve substantially. Further analyses highlighted significant differences between the post-treatment scores of methylprednisolone and those of IVIG or rituximab. These findings suggest that IVIG and rituximab are superior treatment options over steroids alone for managing autoimmune encephalitis in pediatric patients.

Conflicts of interest: No disclosure of conflicts of interests.

Authors' affiliation

Dr. Sameen Qureshi, Fellow Pediatric Neurology
Dr. Amber Shabir, Fellow Pediatric Neurology
Prof. Tipu Sultan, Professor of Pediatric Neurology
Dr. Javeria Raza Alvi, Assistant Professor

Department of Pediatric Neurology, University of Child Health Sciences, The Children's Hospital, Lahore

REFERENCES

1. Leypoldt F, Wandinger KP, Bien CG, Dalmau J. Autoimmune encephalitis. European neurological review. 2013;8(1):31.
2. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. Journal of child neurology. 2012 Nov;27(11):1460-9.
3. Dale RC, Gorman MP, Lim M. Autoimmune encephalitis in children: clinical phenomenology, therapeutics, and emerging challenges. Current Opinion in Neurology. 2017 Jun 1;30(3):334-44.
4. Garg D, Mohammad SS, Sharma S. Autoimmune encephalitis in children: an update. Indian Pediatrics. 2020 Jul;57(7):662-70.
5. Uy CE, Binks S, Irani SRJPN. Autoimmune encephalitis: clinical spectrum and management. 2021;21(5):412-23.
6. Newman M, Blum S, Wong R, Scott J, Prain K, Wilson R, et al. Autoimmune encephalitis. 2016;46(2):148-57.
7. Patel A, Meng Y, Najjar A, Lado F, Najjar SJBS. Autoimmune Encephalitis: A Physician's Guide to the Clinical Spectrum Diagnosis and Management. 2022;12(9):1130.
8. Joubert B, Kerschen P, Zekeridou A, Desestret V, Rogemond V, Chaffois M-O, et al. Clinical spectrum of encephalitis associated with antibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor: case series and review of the literature. 2015;72(10):1163-9
9. Seo JH, Lee Y-J, Lee KH, Gireesh E, Skinner H, Westerveld MJC, et al. Autoimmune encephalitis and epilepsy: evolving definition and clinical spectrum. 2020;63(8):291.
10. Dubey D, Sawhney A, Greenberg B, Lowden A, Warnack W, Khemani P, et al. The spectrum of autoimmune encephalopathies. 2015;287:93-7.
11. Pilotto A, Masciocchi S, Volonghi I, del Zotto E, Magni E, De Giuli V, et al. The clinical spectrum of encephalitis in COVID-19 disease: the ENCOVID multicentre study. 2020:2020.06. 19.20133991.
12. Goenka A, Jain V, Nariai H, Spiro A, Steinschneider MJPn. Extended clinical spectrum of anti–N-methyl-d-aspartate receptor encephalitis in children: a case series. 2017;72:51-5.
13. van Coevorden-Hameete MH, de Bruijn MA, de Graaff E, Bastiaansen DA, Schreurs MW, Demmers JA, et al. The expanded clinical spectrum of anti-GABABR encephalitis and added value of KCTD16 autoantibodies. 2019;142(6):1631-43.
14. Hiesgen J, Schutte CJSSAMJ. Autoimmune encephalitis: Epidemiology, pathophysiology and clinical spectrum (part 1). 2023;113(3):116-21.
15. Prasad P, Bhargava A, Khichar S, Gupta VKJJoC, Research D. Clinical Spectrum of Autoimmune Encephalitis: Case Series from Western Rajasthan. 2017;11(11).
16. Garg D, Mohammad SS, Sharma S. Autoimmune encephalitis in children: an update. Indian pediatrics. 2020;57:662-70.
17. Deng S, Qiu K, Liu H, Wu X, Lei Q, Lu W. Clinical characteristics and short-term prognosis of autoimmune encephalitis: a single-center cohort study in Changsha, China. Frontiers in Neurology. 2019;10:539.
18. Schumacher LT, Mann AP, MacKenzie JG. Agitation management in pediatric males with anti-N-methyl-D-aspartate receptor encephalitis. Journal of child and adolescent psychopharmacology. 2016;26(10):939-43.
19. Zhang S, Mao C, Li X, Miao W, Teng J. Advances in potential cerebrospinal fluid biomarkers for autoimmune encephalitis: A review. Frontiers in Neurology. 2022;13:746653.
20. Ford B, McDonald A, Srinivasan S. Anti-NMDA receptor encephalitis: a case study and illness overview. Drugs Context. 2019;8:212589-.
21. Hogan J, Perez A, Sellier-Leclerc A-L, Vrillon I, Broux F, Nobili F, et al. Efficacy and safety of intravenous immunoglobulin with rituximab versus rituximab alone in childhood-onset steroid-dependent and frequently relapsing nephrotic syndrome: protocol for a multicentre randomised controlled trial. BMJ Open. 2020;10(9):e037306.
22. Huseynova Terzi L, Akdogan N, Dogan Gunaydin S, Atakan N. Comparison of rituximab and intravenous immunoglobulin in the treatment of autoimmune bullous diseases: Real-life data from a single centre. International Journal of Clinical Practice. 2021;75(12):e14955.