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Original Research Article

Predictors of therapeutic response to monthly pulse IV methylprednisolone in pediatric epileptic encephalopathy: a cohort study

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ABSTRACT

Background: Pediatric epileptic encephalopathies (EE) are severe, drug-resistant epilepsy syndromes that often require adjunctive therapies beyond standard antiseizure medications. Data on predictors of response to intravenous methylprednisolone (IVMP), particularly in low- and middle-income countries, are limited.
Methods: This prospective cohort study at the Department of Paediatric Neurology and the Institute of paediatric neurodisorder and autism (IPNA) at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study period spanned January 2020 to June 2021, included 25 children with EE treated with monthly IVMP at a tertiary care center in Bangladesh. Clinical, electroclinical, and neuroimaging variables were analyzed to identify predictors of seizure response (≥50% reduction) using univariate and multivariate logistic regression.
Results: Sixteen children (64%) responded to IVMP. Responders were more likely to have CSWS (68.8% vs. 0%, p<0.001), normal neuroimaging (88.9% vs. 11.1%, p=0.005), and lower baseline seizure frequency (median 5 vs. 20 seizures/day, p=0.003), and none had cerebral palsy (p=0.003). Multivariate analysis confirmed CSWS (adjusted OR (aOR)=35.12, p=0.003), normal neuroimaging (aOR=18.21, p=0.022), and lower seizure burden (aOR=0.92, p=0.038) as independent predictors of response. Concomitant clobazam use showed an association in univariate analysis but did not remain significant after adjustment.
Conclusions: IVMP is a viable, cost-effective immunotherapy for selected children with EE, particularly those with CSWS, structurally normal neuroimaging, and lower seizure burden. Early recognition of these predictors can guide personalized treatment strategies and optimize outcomes in resource-limited settings.

Keywords: Pediatric epileptic encephalopathy, CSWS, IV methylprednisolone, Predictors, Neuroimaging

INTRODUCTION

Epileptic encephalopathies (EE) comprise a group of devastating pediatric epilepsy syndromes that are defined not only by early-onset, intractable seizures but also by their intrinsic role in contributing to progressive cognitive and behavioral deterioration. These disorders, which include syndromes such as Lennox-Gastaut Syndrome (LGS), West Syndrome, and Continuous Spike-and-Wave during Sleep (CSWS), are marked by characteristic electroclinical features and are frequently refractory to conventional antiepileptic drug (AED) therapy. The

prevalence of pediatric epilepsy globally is estimated to range between 1 to 5 per 10,000 live births, with epileptic encephalopathies constituting a major fraction of pharmacoresistant cases.[1] Despite this significant burden, data from low- and middle-income countries (LMICs), including South Asia and particularly Bangladesh, remain sparse. This scarcity arises from diagnostic limitations, lack of access to electroencephalography (EEG) and neuroimaging, and the severe underrepresentation of these populations in international research cohorts.[2]

Children in LMICs often face profound delays in diagnosis and limited access to appropriate therapies, with the epilepsy treatment gap in some regions estimated at over 75%.[3] Bangladesh exemplifies this challenge, where epilepsy often remains underreported due to social stigma, limited public awareness, and minimal pediatric neurology infrastructure.[4] The consequences of delayed intervention in EE are particularly detrimental, as the epileptiform activity itself is thought to exacerbate neurodevelopmental regression a phenomenon that distinguishes encephalopathic epilepsies from other seizure disorders. Consequently, early and targeted treatment is essential for optimizing both seizure control and cognitive outcomes. Emerging evidence has shifted attention toward the immune and inflammatory mechanisms underlying certain forms of EE, particularly CSWS and West Syndrome.

The presence of neuroinflammation, immune dysregulation, and abnormal cytokine profiles in affected children has provided a compelling rationale for the use of immunomodulatory therapy, particularly corticosteroids.[5] Among these, Intravenous methylprednisolone (IVMP) has gained attention as a promising intervention due to its affordability, rapid onset of action, and favorable safety profile in short-term pulse therapy. In contrast to ACTH or IVIG, both of which are expensive and logistically demanding, IVMP represents a more feasible option in resource-constrained settings.[6] Studies suggest that immunotherapy not only reduces seizure burden but may also improve cognitive trajectories and prevent long-term neurological sequelae in responsive subgroups.[5]

Despite growing interest, the predictors of therapeutic response to IVMP in pediatric EE remain poorly understood. Previous investigations have reported variable efficacy, often confounded by heterogeneous inclusion criteria, differences in underlying syndrome type, and inconsistent outcome definitions.[1] Moreover, much of the existing evidence is derived from Western populations, and its applicability to South Asian contexts where genetic, nutritional, and healthcare system variables differ remains unvalidated.[2-7] In particular, there is a lack of granular data from Bangladesh regarding clinical predictors that may stratify responders from non-responders, thus guiding rational immunotherapy use. Identifying such predictors carries both clinical and economic importance. First, it reduces exposure to high-dose steroids in children unlikely to benefit, thereby minimizing potential complications such as weight gain, hyperglycemia, mood disorders, and infection risk. Second, it facilitates more cost-effective care delivery in LMICs, where healthcare resources are scarce and treatment prioritization is essential.[8] Although various clinical features have been proposed as potential predictors including electroclinical syndrome subtype, baseline seizure burden, neuroimaging abnormalities, comorbid conditions such as cerebral palsy or autism, and AED polytherapy their associations have not been consistently validated across studies.[9]

Furthermore, such variables are rarely analyzed together in multivariate models, limiting their clinical utility. Against this backdrop, the present study was designed to explore clinical, neuroimaging, and pharmacologic predictors of seizure response to monthly pulse IVMP in a cohort of children with epileptic encephalopathy in Bangladesh. As one of the first efforts of its kind in this setting, the study aims to fill a critical evidence gap and generate locally relevant data to inform targeted immunotherapy strategies. By doing so, we hope to contribute toward a more individualized, evidence-based approach to managing pediatric EE in resource-limited environments.

METHODS

This was a longitudinal, observational cohort study conducted at the Department of Paediatric Neurology and the IPNA at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study period spanned January 2020 to June 2021, following approval from the Institutional Review Board of BSMMU. Written informed consent was obtained from the parents or legal guardians of all participants before enrollment.

Children younger than 12 years with a clinical diagnosis of developmental and EE were consecutively recruited. Diagnosis required fulfillment of ILAE electroclinical criteria and lack of seizure control despite at least two appropriately selected antiepileptic drugs (AEDs). Children were excluded if they were critically ill, presented in status epilepticus, or had received IV methylprednisolone (IVMP) within the preceding six months. Out of 32 enrolled patients, seven were lost to follow-up during the study (three after the first IVMP cycle and four after the second), leaving a final sample of 25 children who completed all four planned IVMP cycles and were included in the final analysis.

Baseline EEG was performed using 21 scalp electrodes (10-20 system) with both wake and sleep states captured. EEGs were analyzed with the SystemPlus Evolution Micromed software. All patients received monthly pulse IVMP therapy at a dose of 30 mg/kg/day for five consecutive days, repeated at four-week intervals for four cycles, while continuing their background AED regimens

(including sodium valproate, levetiracetam, and/or clobazam). All data were verified for accuracy and analyzed using SPSS version 26. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarized as means±standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. Between-group differences were evaluated using Fisher's exact test for categorical variables and independent t-tests for continuous data. Univariate logistic regression was used to identify potential predictors of seizure response, EEG improvement, and cognitive outcomes. Variables with a p value <0.10 in univariate analyses were entered into multivariate logistic regression models to identify independent predictors, with results reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Statistical significance was defined as $p<0.05$.

RESULTS

Marked differences were observed in the distribution of electroclinical syndromes between responders and non-responders. CSWS was the predominant syndrome among responders (68.8%), whereas Lennox-Gastaut syndrome (LGS) was present in 100% of non-responders and only 25.0% of responders, a statistically significant association ($p<0.001$). One responder (6.3%) was diagnosed with West syndrome, while none of the non-responders fell into this category.

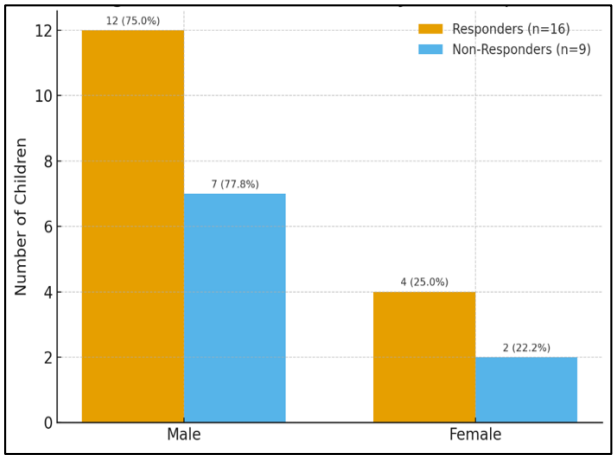

Figure 1: Gender distribution by IVMP response.

A total of 25 children with epileptic encephalopathy were included in the analysis, comprising 16 responders and 9 non-responders to monthly pulse IV methylprednisolone (IVMP) therapy. The mean age at treatment initiation was slightly higher among responders compared to non-responders (6.8±2.5 years vs. 4.5±3.5 years), although this difference did not reach statistical significance ($p=0.08$). Baseline seizure burden was significantly lower in responders compared to non-responders, with a median daily seizure frequency of 5 (IQR: 2-10) versus 20 (IQR: 15–30), respectively ($p=0.003$). Similarly, the presence of cerebral palsy (CP) was exclusively noted among non-responders (55.6% vs. 0.0%, $p=0.003$). Comorbid ADHD and Autism spectrum disorder (ASD) were uncommon and not significantly different between groups.

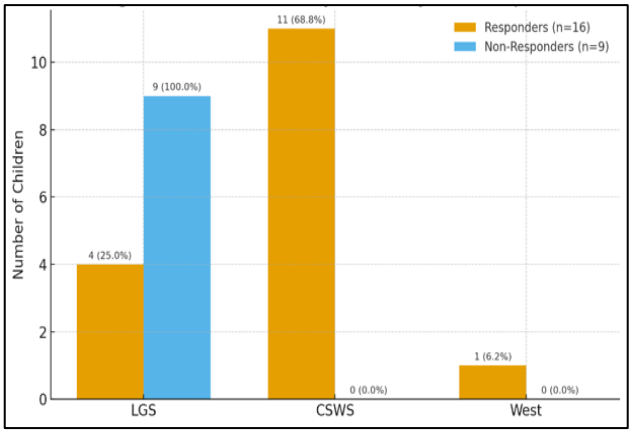

Figure 2: Electroclinical syndrome by IVMP response.

Neuroimaging data, available for 18 children, revealed a strong relationship between imaging findings and treatment response. Normal neuroimaging was observed in 88.9% of responders, compared with only 11.1% of non-responders, while structural abnormalities were detected in 88.9% of non-responders but only 11.1% of responders ($p=0.005$). Analysis of concomitant AED use showed that most children in both groups were receiving sodium valproate (93.8% in responders vs. 77.8% in non-responders, $p=0.26$) and levetiracetam (87.5% vs. 55.6%, $p=0.14$). However, clobazam use was significantly more common among responders (87.5% vs. 44.4%, $p=0.03$).

Univariate logistic regression analysis identified several clinical and imaging variables associated with seizure response (≥50% reduction in seizure frequency) following IVMP therapy. Syndrome subtype was the strongest predictor of treatment response, with all children diagnosed with CSWS responding to IVMP, while none of the children with LGS achieved a response. This resulted in an undefined odds ratio (OR) due to the absence of non-responders in the CSWS group ($p<0.001$), indicating that CSWS was an almost perfect predictor of favorable response in this cohort.

Similarly, the absence of cerebral palsy (CP) was a strong and statistically significant predictor of response, as none of the responders had CP compared with 55.6% of non-responders, producing another undefined OR ($p=0.003$). Normal neuroimaging findings were also highly predictive of response, with an OR of 56.0 (95% CI: 4.5-692.1, $p=0.002$), highlighting the strong association between structurally normal imaging and favorable treatment outcomes. A lower baseline seizure burden was significantly associated with improved response, with an OR of 0.87 (95% CI: 0.78-0.97, $p=0.01$), indicating that each additional daily seizure reduced the odds of response by approximately 13%. Concomitant clobazam

use was also associated with a higher likelihood of response (OR:8.75; 95% CI:1.2-65.0; p=0.03), while concomitant levetiracetam use showed a non-significant trend toward improved response (OR: 5.60; 95% CI: 0.9-34.0; p=0.06). Other variables, including concomitant valproate use (OR:4.29; 95% CI:0.5-39.2; p=0.19), age (OR:1.30; 95% CI:0.96-1.75; p=0.09), and gender (OR:0.86; 95% CI:0.1-5.9; p=0.88) did not demonstrate statistically significant associations with seizure response.

Table 1: Baseline characteristics of the cohort, stratified by seizure response to IVMP.

Variables	Responders (n=16)	Non-responders (n=9)	P value
Age, years (mean±SD)	6.8±2.5	4.5±3.5	0.08
Pre-treatment seizure frequency (/day), median (IQR)	5 (2,10)	20 (15,30)	0.003
Key comorbidities, N (%)			
Cerebral palsy	0 (0.0)	5 (55.6)	0.003
ADHD	1 (6.3)	1 (11.1)	1.00
ASD	0 (0.0)	1 (11.1)	0.35
Neuroimaging (n=18), N (%)			
Normal	8 (88.9)	1 (11.1)	0.005
Abnormal	1 (11.1)	8 (88.9)	
Concomitant AEDS, N (%)			
Sodium valproate	15 (93.8)	7 (77.8)	0.26
Levetiracetam	14 (87.5)	5 (55.6)	0.14
Clobazam	14 (87.5)	4 (44.4)	0.03

Table 2: Univariate analysis of predictors of seizure response (≥50% reduction) to IVMP therapy.

Predictor variables	Odds ratio (OR)	95% confidence interval	P value
Syndrome type (CSWS VS. LGS)	Undefineda	-	<0.001
Normal neuroimaging (yes vs. No)	56.0	4.5-692.1	0.002
Absence of cerebral palsy (yes vs. No)	Undefinedb	-	0.003
Lower pre-treatment seizure burden ^C	0.87	0.78-0.97	0.01
Concomitant clobazam use (yes vs. No)	8.75	1.2-65.0	0.03
Concomitant levetiracetam use (yes vs. No)	5.60	0.9-34.0	0.06
Concomitant valproate use (yes vs. No)	4.29	0.5-39.2	0.19
Age (per year increase)	1.30	0.96-1.75	0.09
Gender (male vs. Female)	0.86	0.1-5.9	0.88

a. Undefined OR: The Odds ratio is undefined because all 11 patients with CSWS responded (creating a "0" in the non-responder cell for CSWS). This is an infinite OR, powerfully indicating CSWS is a near-perfect predictor of response compared to LGS in this cohort.
b. Undefined OR: Similarly, the absence of Cerebral Palsy is a perfect predictor of response in this cohort (0 responders had CP), leading to an infinite OR.

Table 3: Multivariate logistic regression analysis of independent predictors of seizure response (≥50% reduction) to IVMP therapy.

Predictor variables	Adjusted odds ratio (aOR)	95% confidence interval	P value
Syndrome type (CSWS vs. LGS)	35.12	3.45-357.41	0.003
Normal neuroimaging (yes vs. No)	18.21	1.52-218.32	0.022
Concomitant clobazam use (yes vs. No)	5.80	0.65-51.92	0.115
Lower pre-treatment seizure burden (per 1-unit decrease/day)	0.92	0.85-0.99	0.038

Multivariate logistic regression identified syndrome type, neuroimaging findings, and baseline seizure burden as independent predictors of seizure response to IVMP therapy. Children diagnosed with CSWS had markedly higher odds of achieving a ≥50% reduction in seizure frequency compared to those with LGS, with an adjusted odds ratio (aOR) of 35.12 (95% CI:3.45-357.41; p=0.003). Similarly, having normal neuroimaging independently predicted a favorable response (aOR: 18.21; 95% CI:1.52-218.32; p=0.022). A lower baseline seizure burden remained a significant independent predictor of seizure reduction, with an aOR of 0.92 (95%

CI: 0.85-0.99; p=0.038), indicating that each additional daily seizure slightly decreased the likelihood of response. Concomitant clobazam use, while associated with higher odds of response in univariate analysis, did not reach statistical significance in the multivariate model (aOR:5.80; 95% CI:0.65-51.92; p=0.115), suggesting that its predictive value was confounded by other clinical variables.

DISCUSSION

This study explored predictors of therapeutic response to monthly IVMP in children with EE. Our findings highlight several clinical and neuroimaging markers that distinguished responders from non-responders, offering practical implications for treatment selection in resource-limited settings. The most prominent result was the syndrome-specific response pattern. Children with continuous spike-and-wave during sleep (CSWS) uniformly responded to IVMP, whereas all cases of Lennox gastaut syndrome (LGS) were non-responders. This aligns with previous evidence that CSWS often shows favorable outcomes with corticosteroid therapy, likely reflecting its immunoinflammatory underpinnings.[10] By contrast, LGS is characterized by multifactorial etiologies, including structural and genetic causes, which contribute to its marked pharmacoresistance.[11] The multicenter RESCUE ESES trial further demonstrated superior short-term seizure and cognitive outcomes with corticosteroids compared to clobazam in children with EE-SWAS, supporting the preferential role of steroids in CSWS-like epileptic encephalopathies.[12] Neuroimaging status emerged as another independent predictor of IVMP response.

Responders were far more likely to have normal MRI findings, whereas non-responders typically demonstrated structural abnormalities. This observation is consistent with reviews emphasizing that intact structural substrates predict better responses to immunotherapy, while fixed lesions often drive persistent epileptogenesis despite aggressive treatment.[13,14] Similarly, cerebral palsy was exclusive to non-responders in our cohort, underscoring how comorbid motor and developmental disabilities usually markers of underlying structural injury are associated with poor treatment outcomes.[15] A further important finding was the role of baseline seizure burden.

Children with lower daily seizure frequencies were more likely to respond, while each incremental increase in seizure load reduced the odds of favorable response. This reinforces the concept that disease severity influences therapeutic efficacy, with early intervention before the establishment of high-frequency epileptiform activity offering better potential for neurocognitive preservation.[10] It also highlights the need for timely identification and initiation of immunotherapy in suitable patients. In terms of concomitant Antiepileptic drug (AED) use, clobazam was more common among responders in univariate analysis, though it did not retain independent predictive value after adjustment. The RESCUE ESES trial showed that clobazam does provide benefit in EE-SWAS, but that corticosteroids remain superior for seizure and cognitive outcomes.[12] This suggests clobazam may play a supportive role but is unlikely to independently determine steroid responsiveness. Meanwhile, sodium valproate and levetiracetam, commonly used in refractory pediatric epilepsy, showed no significant association with treatment outcome in our cohort, consistent with their variable effectiveness across electroclinical subtypes.[11]

Taken together, our study adds to the growing body of literature that underscores the importance of syndrome subtype, neuroimaging integrity, absence of cerebral palsy, and seizure burden as key predictors of immunotherapy response in pediatric EE. These results reinforce the need for individualized, syndrome-driven treatment strategies, especially in LMICs where IVMP offers a cost-effective and accessible alternative to ACTH or IVIG.[13] By identifying reliable predictors, clinicians can better target therapy, minimize unnecessary steroid exposure, and allocate limited healthcare resources more effectively.

Limitations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

This prospective cohort study provides evidence that the therapeutic response to monthly IVMP in pediatric EE is strongly influenced by electroclinical and clinical characteristics. Children with CSWS, normal neuroimaging, absence of cerebral palsy, and lower baseline seizure burden were significantly more likely to achieve meaningful seizure reduction. These findings support a syndrome-driven, individualized approach to immunotherapy, particularly in resource-limited settings such as Bangladesh, where IVMP offers a cost-effective alternative to ACTH or IVIG. Incorporating these predictors into clinical decision-making can optimize treatment outcomes, reduce unnecessary steroid exposure, and inform future clinical trials to validate and refine predictive models in diverse populations.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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