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Original Article

Efficacy of ACTH therapy in treating infantile epileptic spasm syndrome and its effect on Kramer score

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Abstract: Objective: To compare the clinical efficacy and safety of adrenocorticotropic hormone (ACTH) combined with topiramate versus topiramate monotherapy in treating Infantile Epileptic Spasm Syndrome (IESS), and to explore the risk factors for relapse. Methods: This retrospective cohort study included 185 IESS pediatric patients treated at Yan'an People's Hospital between April 2018 and January 2024. Patients were divided into a control group (n=95, topiramate monotherapy) and an observation group (n=90, ACTH combined with topiramate) based on their treatment regimen. Propensity score matching (PSM) was employed to balance baseline differences. Outcomes compared between the groups included spasm control rates, electroencephalogram (EEG) improvement, changes in functional scores, and incidence of adverse reaction. Multivariate logistic regression was used to identify independent risk factors for relapses. Results: The observation group demonstrated significantly higher rates of complete spasm control (75.56% vs. 50.53%) and complete EEG improvement (76.67% vs. 54.74%) compared to the control group (P<0.01). Post-treatment, the observation group showed more significant improvements in developmental quotient (DQ), motor index (MI), and Kramer scores (P<0.01). Multivariate analysis identified structural etiology (OR=3.12), monotherapy (OR=2.54), and higher Kramer scores (OR=1.45) as independent risk factors for relapse (all P<0.01). The incidence of adverse reactions did not differ significantly between groups (34.44% vs. 29.47%, P=0.468). Conclusion: ACTH combined with topiramate offers superior efficacy for spasm control, EEG improvement, and neurological function recovery compared to topiramate monotherapy, without increasing adverse reactions. Structural etiology, monotherapy, and Kramer scores are independent predictors for relapse.

Keywords: Infantile convulsive syndrome, adrenocorticotropic hormone, topiramate, combination therapy

Introduction

Infantile Epileptic Spasms Syndrome (IESS) is a severe neurodevelopmental disorder typically occurring in infants between 3 and 12 months of age, characterized by myoclonic spasms, distinctive electroencephalographic (EEG) abnormalities, and significant neurodevelopmental delays [1, 2]. Infantile Spasms, or IESS, are a tough nut to crack when it comes to epileptic seizures. What makes IESS particularly nasty is the serious hit it deals to the developing brain, frequently causing lasting problems with thinking and behavior [3]. IESS affects about one baby out of every 2,000 to 4,000 born. Due to its rapid onset and potential for irreversible brain damage, early diagnosis and timely intervention are critical [4]. Without timely intervention, IESS may progress to other intractable epilepsy syndromes and result in profound cognitive and behavioral deficits [5].

Currently, pharmacologic intervention remains the primary treatment strategy for IESS, with antiepileptic drugs (AEDs) (e.g., Topiramate) and adrenocorticotropic hormone (ACTH) being commonly used [6]. Although topiramate is not among the traditional first-line agents, it has gained increasing clinical attention due to its favorable pharmacologic profile. Topiramate acts through multiple mechanisms to suppress abnormal neuronal excitability and epileptiform discharges [7]. Compared with conventional AEDs, it is associated with better tolerability, a lower incidence of adverse effects, and reduced treatment cost [8]. However, its efficacy as

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monotherapy for the initial management of IESS remains suboptimal in a substantial subset of patients [9].

Another established treatment for IESS is ACTH therapy has been widely used in clinical practice due to its effectiveness in controlling spasms [10]. ACTH works by modulating the immune system, which in turn helps regulate abnormal brain activity and alleviate the spasms [11]. However, ACTH isn't without its challenges. Approximately 30-40% of patients do not respond to ACTH. Additionally, ACTH can cause side effects like hyperglycemia, weight gain, immunosuppression, and an increased risk of infections, which can be tough for some children to tolerate [12]. Furthermore, ACTH therapy usually requires prolonged administration and this puts a financial burden on both families and healthcare systems [13].

Given these limitations, researchers have increasingly explored combination treatments. The rationale behind combining ACTH and topiramate is straightforward: ACTH is used to quickly control spasms, while topiramate is purposed for long-term maintenance to prevent relapse and stabilize the condition. This combination approach may also reduce the frequency of adverse effects associated with ACTH treatment [14]. While this strategy appears promising, there is insufficient robust evidence comparing the ACTH-topiramate combination to monotherapy with either drug [15].

This study aimed to evaluate the effectiveness of combining ACTH and topiramate in treating IESS, focusing on spasm control, brain development, and disease relapse. The goal is to provide clinicians with evidence to inform treatment decisions, ultimately improving outcomes for children with IESS and paving the way for future research in this field.

Patients and methods

Sample size calculation

Sample size was calculated based on the study by Wanigasinghe et al. [16], using the formula for comparison of two independent proportions:

$$n = \frac{\left(Z_{\alpha/2}\sqrt{2\bar{p}(1-\bar{p})} + Z_{\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right)^2}{\delta^2}$$

where α=0.05 (two-sided), corresponding to $Z\alpha/2$=1.96, 1-β=80%, corresponding to $Z\beta$=0.84. Based on estimated proportions of p_1=0.4375, p_2=0.1837, with a minimal detectable difference δ=0.2538, the calculated sample size was 52 per group. Considering a 10% loss or dropout, required sample size per group was increased to 57, for a total of 114 cases.

General information

A retrospective cohort analysis was conducted on clinical data from 185 IESS pediatric patients at Yan'an People's Hospital between April 2018 and January 2024. The patients were divided into a control group (n=95, topiramate monotherapy) and an observation group (n=90, topiramate monotherapy + ACTH). This study was approved by the Ethics Committee of Yan'an People's Hospital.

Inclusion and exclusion criteria

Inclusion Criteria: Diagnosis of IESS was based on clinical presentation, including typical myoclonic spasms and characteristic EEG findings [1]; age between 2 and 24 months; First episode of IESS, with no prior use of antiepileptic drugs or steroid treatments; and complete clinical data available.

Exclusion Criteria: Congenital heart disease or major organ dysfunction (e.g., liver or renal failure); Severe immune system disorders; diagnosis of other types of epilepsy (e.g., focal or generalized epilepsy) that met treatment criteria for those conditions; severe intellectual disability or other congenital neurological abnormalities that would prevent adquate evaluation of treatment response.

Treatment protocol

Control Group: Patients in the control group received topiramate (Xian Janssen Pharmaceutical Ltd., Drug Approval No.: H20020555). The initial dose was 0.5-1.0 mg/(kg·d), which was gradually increased based on the patient's clinical response. The increment was about 0.5-1.0 mg/(kg·d) each week, and a target maintenance dose ranging from 3.3-14 mg/(kg·d) for 3 months per treatment cycle.

Observation Group: Patients in the observation group received a combination of ACTH

(Shanghai Pharmaceutical First Biochemical Pharmaceutical Co., Drug Approval No.: H310-22101) and topiramate. ACTH was administered at an initial dose of 2 IU/(kg·d), dissolved in 100 mL of 5% glucose solution, and infused intravenously over 6-8 hours. If spasms persisted after two weeks, the dose was increased to 4 IU/(kg·d). After two weeks without seizures, Topiramate treatment was initiated, following the same protocol as in the control group, with a 3-month treatment cycle. Both groups were treated for one full cycle.

Data collection

Clinical data were collected from an electronic medical records system. The data included:

Baseline clinical features: Age, sex, disease duration, etiology classification (structural/non-structural), delivery method, and other demographic and medical history data were extracted from the first visit records.

Treatment response indicators: Seizure control (complete control defined as seizure cessation for >28 days, partial control as a ≥50% reduction in seizure frequency) and EEG improvement (assessed according to the modified Hypsarrhythmia scoring system).

Functional prognosis indicators: Developmental Quotient (DQ), Mental Index (MI), and Kramer scores were extracted from follow-up records to assess neurodevelopmental status.

Safety data: Laboratory reports and medical records were reviewed for adverse events such as electrolyte disturbances and weight changes.

Relapse indicators: Follow-up records were reviewed to determine the time and frequency of spasm relapse within one year.

All data were independently extracted and verified by two pediatric neurologists using standardized forms. Any discrepancies were resolved through third-party expert arbitration to ensure accuracy and consistency.

Functional scoring

Developmental quotient (DQ): This index evaluates cognitive, language, motor, and social adaptability skills, with a score range of 0-100. A score ≥85 indicates normal development, 70-84 suggests borderline status, and <70 indicates developmental delay [17].

Mental index (MI): This measures intellectual development, with a score range of 50-150. A score ≥90 is considered normal, 70-89 is borderline, and <70 indicates intellectual disability [18].

Kramer score: This quantifies the severity of epileptic encephalopathy, with scores ranging from 0-15. Scores ≤5 indicate good control, while scores ≥10 suggest poor prognosis [19].

Effectiveness assessment criteria

Seizure Control: Complete control: Seizures are fully terminated for more than 28 days. Partial control: Seizure frequency is reduced by ≥50%. Ineffective: Seizure frequency is reduced by <50% or no significant improvement [20].

EEG Improvement: Complete control: Hypsarrhythmia completely disappears on EEG. Effective: Significant reduction in EEG abnormalities. Ineffective: No significant improvement in EEG abnormalities [20].

Follow-up

All patients included in the study underwent a systematic follow-up for one year, through scheduled outpatient evaluations at 3, 6, and 12 months post-treatment.

Outcome measurements

Primary outcomes: Analysis of treatment efficacy and improvements in functional scores before and after propensity score matching (PSM) [5]. Secondary Outcomes: The rates of adverse events and relapse were compared between the research and control groups before and after PSM, with logistic regression analysis used to identify factors influencing relapse.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 and R software (version 4.3.1). Normally distributed data were presented as mean ± standard deviation ($\bar{x} \pm s$), with intergroup comparisons conducted using independent samples t-tests and intragroup comparisons using

Table 1. Comparison of the baseline data of the young children

Indicator	Total	Control group (n=95)	Observation group (n=90)	Statistical Value	*P* value
Gender					
Male	103 (55.68%)	54 (56.84%)	49 (54.44%)	0.108	0.743
Female	82 (44.32%)	41 (43.16%)	41 (45.56%)		
Primiparity					
Yes	93 (50.27%)	47 (49.47%)	46 (51.11%)	0.050	0.824
No	92 (49.73%)	48 (50.53%)	44 (48.89%)		
Mode of Delivery					
Vaginal delivery	119 (64.32%)	59 (62.11%)	60 (66.67%)	0.419	0.517
Cesarean section	66 (35.68%)	36 (37.89%)	30 (33.33%)		
Abnormal Labor					
Yes	178 (96.22%)	92 (96.84%)	86 (95.56%)	0.210	0.647
No	7 (3.78%)	3 (3.16%)	4 (4.44%)		
Etiology					
Structural	84 (45.41%)	42 (44.21%)	42 (46.67%)	0.112	0.737
Other	101 (54.59%)	53 (55.79%)	48 (53.33%)		
Maternal Miscarriage History					
Yes	29 (15.68%)	17 (17.89%)	12 (13.33%)	0.727	0.394
No	156 (84.32%)	78 (82.11%)	78 (86.67%)		
Child's Age (Months)	15.27±3.26	16.00±3.05	14.50±3.31	3.207	0.002
Disease Duration (Months)	7.00 (3.00)	8.00 (3.00)	6.00 (2.75)	5.006	<0.001
Maternal Age (Years)	26.00 (4.00)	26.00 (4.00)	26.00 (2.75)	0.369	0.712

Note: Other causes include genetic, metabolic, and unclear. Abnormal labor process includes premature birth and expired labor.

paired t-tests. Non-normally distributed data were expressed as median (interquartile range) [M (IQR)], with intergroup comparisons using the Mann-Whitney U test and intragroup comparisons using the Wilcoxon signed-rank test. Categorical data were presented as counts (percentages), with intergroup comparisons conducted using the Chi-square test.

To control for baseline confounding factors, propensity score matching (PSM) was performed using the MatchIt, optmatch, and cobalt packages in R, with a caliper value of 0.02 for nearest-neighbor matching at a 1:1 ratio. After matching, standardized mean differences were assessed to evaluate covariate balance.

Univariate and multivariate logistic regression analyses were performed using SPSS 27.0. Potential influencing factors were screened through univariate analysis (P<0.05), and independent factors were identified in a multivariate logistic regression model. A Forest plot was generated using R's forestplot package to display odds ratios (ORs) and their 95% confidence intervals. All statistical tests were two-sided, and P<0.05 was considered significant.

Results

Comparison of baseline information between the observation and control groups (before PSM)

No significant differences were observed between the two groups in terms of gender (P=0.743), primiparity (P=0.824), mode of delivery (P=0.517), abnormal labor (P=0.647), etiology (P=0.737), maternal history of miscarriage (P=0.394), or maternal age (P=0.712). However, the observation group had significantly lower age (P=0.002) and shorter disease duration (P<0.001) compared to the control group, as shown in **Table 1**.

Comparison of seizure control and EEG improvement the observation and control groups (before PSM)

The observation group demonstrated significantly higher rates of both complete and effec-

Table 2. Comparison of the effect of spastic seizure control

Group	Complete Control	Effective Control	Ineffective	Total Effective Rate
Control group (n=95)	48 (50.53%)	42 (44.21%)	5 (5.26%)	90 (94.74)
Observation group (n=90)	68 (75.56%)	20 (22.22%)	2 (2.22%)	88 (97.78)
χ^2 value	12.380	10.028		1.174
P value	0.001	0.002		0.279

Table 3. Comparison of the EEG spasm improvement

Group	Complete Control	Effective Control	Ineffective	Total Effective Rate
Control group (n=95)	52 (54.74%)	38 (40.00%)	5 (5.26%)	90 (94.74)
Observation group (n=90)	69 (76.67%)	20 (22.22%)	1 (1.11%)	89 (98.89)
χ^2 value	9.823	6.786		2.539
P value	0.002	0.009		0.111

Table 4. Effects of spasticity frequency before and after treatmen

Group	Seizure Frequency		Z value	*P* value
	Before Treatment	After Treatment		
Control group (n=95)	9.00 (3.00)	1.00 (1.00)	8.483	<0.001
Observation group (n=90)	9.00 (3.75)	1.00 (0.00)	8.253	<0.001
Z value	0.746	6.342		
P value	0.456	<0.001		

tive control (**Table 2**). The complete control rate in the observation group was 75.56%, significantly higher than 50.53% in the control group (P=0.001). However, the effective control rate was significantly lower in the observation group (P=0.002). The overall effective rate for the observation group was 97.78%, which is comparable to 94.74% in the control group (P=0.279).

In terms of EEG improvement (**Table 3**), the observation group showed a complete control rate of 76.67% and an effective control rate of 22.22%, and those of the control group were 54.74% and 40.00% (P=0.002, P=0.009). The overall effective rate for the observation group was 98.89%, comparable to 94.74% in the control group (P=0.111).

Comparison of seizure frequency between the observation and control groups (before PSM)

Before treatment, no significant difference in seizure frequency was observed between the two groups (P=0.456). After treatment, both groups showed significant reductions in seizure frequency (both P<0.001). The difference in seizure frequency between the groups post-treatment was also significant (P<0.001), as shown in **Table 4**.

Comparison of functional scores between the observation and control groups before and after treatment (before PSM)

Before treatment, no significant differences were found in functional scores: DQ score (P=0.869), MI score (P=0.844), or Kramer score (P=0.142). After treatment, DQ and MI scores significantly increased in both groups, while Kramer scores significantly decreased (all P<0.001). Notably, the observation group demonstrated significantly higher DQ (P<0.001) and MI (P<0.001) scores and significantly lower Kramer scores (P=0.010) compared to the control group. The details are shown in **Table 5**.

Comparison of adverse reactions between the observation and control groups (before PSM)

There were no significant differences in adverse reaction rates regarding irritability (P=0.369), increased appetite (P=0.574), gastrointestinal reactions (P=0.916), rashes (P=0.574), arrhythmias (P=0.695), or electrolyte disturbances

Table 5. Analysis of functional score changes

Group	DQ score		Z value	*P* value
	Before Treatment	After Treatment		
Control group (n=95)	68.85±3.25	90.00 (3.00)	11.604	<0.001
Observation group (n=90)	68.93±3.39	95.00 (3.00)	11.614	<0.001
t/Z value	0.165	9.208		
P value	0.869	<0.001		
Group	MI score		Z value	*P* value
	Before Treatment	After Treatment		
Control group (n=95)	70.71±3.05	93.00 (3.00)	11.927	<0.001
Observation group (n=90)	70.79±2.72	96.00 (4.00)	11.931	<0.001
t/Z value	0.197	8.160		
P value	0.844	<0.001		
Group	Kramer score		Z value	*P* value
	Before Treatment	After Treatment		
Control group (n=95)	10.00 (2.00)	6.00 (3.00)	7.779	<0.001
Observation group (n=90)	9.50 (3.00)	5.00 (3.00)	7.982	<0.001
Z	1.467	2.582		
P	0.142	0.010		

Note: DQ: Developmental Quotient, MI: Mental Index.

(P=0.076) between the groups, as shown in **Table 6**.

Comparison of baseline information between the observation and control groups (after PSM)

After PSM, the baseline data of the control and observation groups were compared. No significant differences were found in terms of gender (P=0.247), primiparity (P=0.491), mode of delivery (P=0.629), abnormal labor (P=0.152), etiology (P=1.000), maternal history of miscarriage (P=0.761), maternal age (P=1.000), patient age (P=0.794), or disease duration (P=0.716) between the two groups, as shown in **Table 7**.

Baseline characteristics of relapse and non-relapse groups after PSM

A propensity score matching analysis was performed using a caliper value of 0.02. The Love plot (**Figure 1A**) shows that, after matching, all standardized mean differences for covariates were less than 0.1, indicating good matching. The QQ plot (**Figure 1B**) visually demonstrates the improvement in covariate distribution before and after matching, with the covariate distributions of the relapse and non-relapse groups becoming more similar after matching. Before matching, the sample size was 185 (95 in the control group, 90 in the observation group, 55 in the relapse group, and 130 in the non-relapse group). After matching, 76 cases were retained (38 in the control group, 38 in the observation group, 20 in the relapse group, and 56 in the non-relapse group). The matching model used logit regression to calculate the propensity scores, with sampling without replacement to ensure matching quality.

Comparison of seizure control and EEG improvement the observation and control groups (after PSM)

After PSM, the efficacy of ACTH in seizure control and EEG improvement was evaluated. As shown in **Table 8**, complete seizure control rate was 78.95%, significantly higher than 42.11% in the control group (P=0.001). However, the effective control rate was significantly lower in the observation group (P=0.001). No significant difference in total effective rate was found between the two groups (P>0.999). Regarding EEG improvement (**Table 9**), no significant difference was found in total effective rate between the two groups (P=0.152).

Comparison of seizure frequency between the observation and control groups (after PSM)

Before treatment, no significant difference in seizure frequency was observed between the

Table 6. Comparison of adverse effects in the PSM and control groups

Group	Irritability	Increased Appetite	Gastrointestinal Reactions	Electrolyte Disturbances	Rash	Arrhythmia	Total
Control group (n=95)	2 (2.11%)	6 (6.32%)	7 (7.37%)	4 (4.21%)	6 (6.32%)	3 (3.16%)	28 (29.47%)
Observation group (n=90)	4 (4.44%)	4 (4.44%)	7 (7.78%)	10 (11.11%)	4 (4.44%)	2 (2.22%)	31 (34.44%)
χ^2	0.806	0.317	0.011	3.146	0.317	0.154	0.526
P	0.369	0.574	0.916	0.076	0.574	0.695	0.468

Table 7. Comparison of baseline data of children after PSM

Indicator	Total	Control group (n=38)	Observation group (n=38)	Statistical Value	*P* value
Gender					
Male	43 (56.58%)	19 (50.00%)	24 (63.16%)	1.339	0.247
Female	33 (43.42%)	19 (50.00%)	14 (36.84%)		
Primiparity					
Yes	37 (48.68%)	17 (44.74%)	20 (52.63%)	0.474	0.491
No	39 (51.32%)	21 (55.26%)	18 (47.37%)		
Mode of Delivery					
Vaginal delivery	50 (65.79%)	24 (63.16%)	26 (68.42%)	0.234	0.629
Cesarean section	26 (34.21%)	14 (36.84%)	12 (31.58%)		
Abnormal Labor					
Yes	74 (97.37%)	38 (100.00%)	36 (94.74%)	2.054	0.152
No	2 (2.63%)	0 (0.00%)	2 (5.26%)		
Etiology					
Structural	34 (44.74%)	17 (44.74%)	17 (44.74%)	0.000	1.000
Other	42 (55.26%)	21 (55.26%)	21 (55.26%)		
Maternal Miscarriage History					
Yes	13 (17.11%)	6 (15.79%)	7 (18.42%)	0.093	0.761
No	63 (82.89%)	32 (84.21%)	31 (81.58%)		
Child's Age (Months)	15.41±3.05	15.50±2.80	15.32±3.32	0.261	0.794
Disease Duration (Months)	6.71±1.87	6.63±1.96	6.79±1.80	-0.365	0.716
Maternal Age (Years)	26.11±2.54	26.11±3.06	26.11±1.94	0.000	1.000

Note: Other causes include genetic, metabolic, and unclear. Abnormal labor process includes premature birth and expired labor.

two groups (P=0.426). After treatment, both groups showed a significant reduction in seizure frequency (both P<0.001). The difference in seizure frequency between the observation and control groups after treatment was significant (P<0.001), as shown in **Table 10**.

Comparison of functional scores between the observation and control groups before and after treatment (after PSM)

Before treatment, there were no significant differences in DQ (P=0.838) and MI (P=0.161) scores between the two groups. The difference in Kramer scores between two groups approached significance (P=0.056). After treatment, DQ and MI scores increased significantly in both groups, while Kramer scores decreased significantly (all P<0.001). Notably, the observation group demonstrated significantly higher DQ (P<0.001) and MI (P<0.001) scores and significantly lower Kramer scores (P=0.028) compared to the control group, as shown in **Table 11**.

Comparison of adverse reactions between the observation and control groups (after PSM)

There were no significant differences in adverse reaction rates between the two groups (34.21%

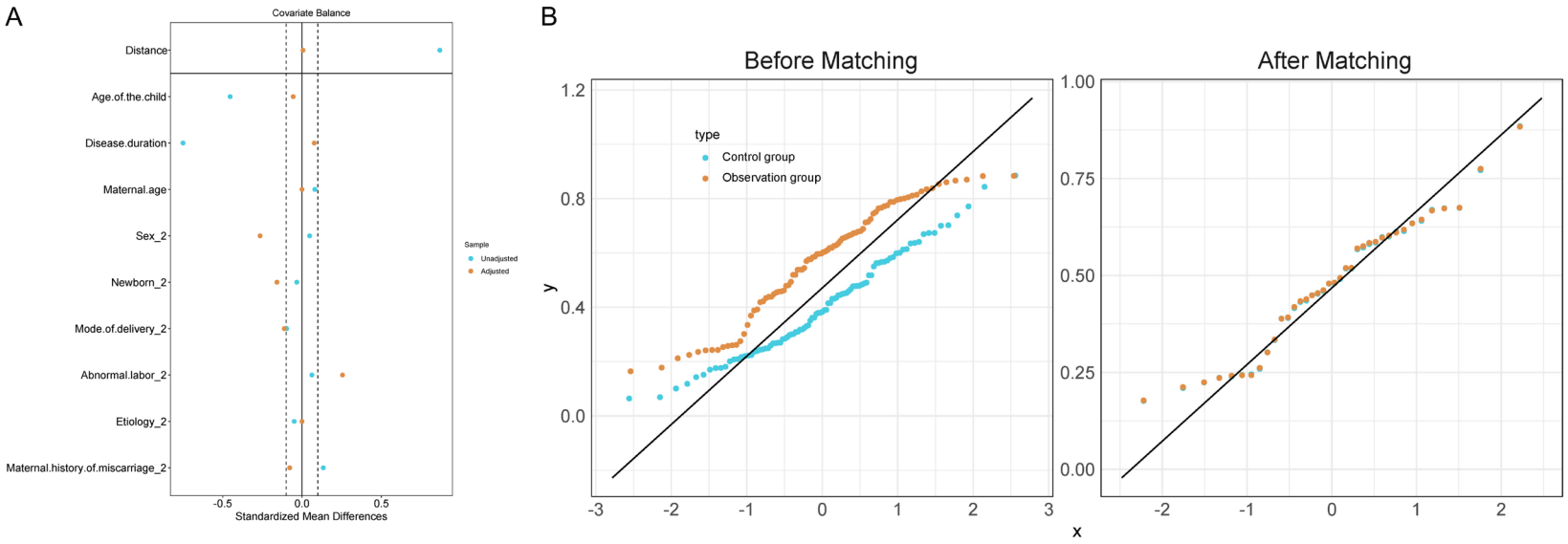

Figure 1. Assessment of score matching quality. A. Love plot Change of standardized mean difference before and after matching. B. QQ chart shows the comparison of the distribution of covariates before and after matching.

Table 8. Comparison of the effects of spastic seizure control after PSM

Group	Complete Control	Effective Control	Ineffective	Total Effective Rate
Control group (n=38)	16 (42.11%)	21 (55.26%)	1 (2.63%)	37 (97.37%)
Observation group (n=38)	30 (78.95%)	7 (18.42%)	1 (2.63%)	37 (97.37%)
χ^2 value	10.794	11.083		<0.001
P value	0.001	0.001		>0.999

Table 9. Comparison of the improvement in EEG spasticity after PSM

Group	Complete Control	Effective Control	Ineffective	Total Effective Rate
Control group (n=38)	24 (63.16%)	12 (31.58%)	2 (5.26%)	36 (94.74%)
Observation group (n=38)	30 (78.95%)	8 (21.05%)	0 (0.00%)	38 (100.00%)
χ^2 value	2.303	1.085		2.054
P value	0.129	0.297		0.152

Table 10. Analysis of seizure frequency changes after PSM

Group	Seizure Frequency		Z value	*P* value
	Before Treatment	After Treatment		
Control group (n=38)	9.00 (2.00)	1.00 (1.00)	5.382	<0.001
Observation group (n=38)	9.00 (2.00)	1.00 (0.00)	5.392	<0.001
Z value	0.795	4.596		
P value	0.426	<0.001		

Table 11. Analysis of functional score changes after PSM

Group	DQ score		t	*P* value
	Before Treatment	After Treatment		
Control group (n=38)	69.00±3.39	90.32±2.67	-29.338	<0.001
Observation group (n=38)	69.16±3.32	95.18±2.75	-39.099	<0.001
t	-0.205	-7.827		
P value	0.838	<0.001		
Group	MI score		t	*P* value
	Before Treatment	After Treatment		
Control group (n=38)	70.84±3.18	92.55±1.87	-37.719	<0.001
Observation group (n=38)	69.87±2.80	95.21±2.78	-41.177	<0.001
t	1.418	-4.888		
P value	0.161	<0.001		
Group	Kramer score		Z value/t	*P* value
	Before Treatment	After Treatment		
Control group (n=38)	10.00 (3.00)	6.00 (2.75)	4.989	<0.001
Observation group (n=38)	9.00 (2.00)	5.00 (3.00)	12.208	<0.001
Z value	1.908	2.194		
P value	0.056	0.028		

Note: DQ: Developmental Quotient, MI: Mental Index.

vs. 31.58%, P=0.807), specifically, irritability (P=0.152), increased appetite (P=0.644), gastrointestinal reactions (P=0.304), rashes (P=0.644), arrhythmias (P=0.314), and electrolyte disturbances (P=0.455), as shown in **Table 12**.

Comparison of baseline data between relapse and non-relapse groups before PSM

The patients were followed for one year, revealing a relapse rate of 29.76% (55/185). Before

Table 12. Comparison of adverse effects between treatment and control groups after PSM

Group	Irritability	Increased Appetite	Gastrointestinal Reactions	Electrolyte Disturbances	Rash	Arrhythmia	Total
Control group (n=38)	0 (0.00%)	3 (7.89%)	3 (7.89%)	3 (7.89%)	2 (5.26%)	1 (2.63%)	12 (31.58%)
Observation group (n=38)	2 (5.26%)	2 (5.26%)	1 (2.63%)	5 (13.16%)	3 (7.89%)	0 (0.00%)	13 (34.21%)
χ^2 value	2.054	0.214	1.056	0.559	0.214	1.013	0.060
P value	0.152	0.644	0.304	0.455	0.644	0.314	0.807

Table 13. Comparison of baseline data for children with recurrence before PSM

Indicator	Total	Relapse Group (n=55)	Non-Relapse Group (n=130)	Statistical Value	*P* value
Gender					
Male	103 (55.68%)	30 (54.55%)	73 (56.15%)	0.041	0.840
Female	82 (44.32%)	25 (45.45%)	57 (43.85%)		
Primiparity					
Yes	93 (50.27%)	24 (43.64%)	69 (53.08%)	1.378	0.240
No	92 (49.73%)	31 (56.36%)	61 (46.92%)		
Mode of Delivery					
Vaginal delivery	119 (64.32%)	34 (61.82%)	85 (65.38%)	0.214	0.643
Cesarean section	66 (35.68%)	21 (38.18%)	45 (34.62%)		
Abnormal Labor					
Yes	178 (96.22%)	53 (96.36%)	125 (96.15%)	0.005	0.946
No	7 (3.78%)	2 (3.64%)	5 (3.85%)		
Etiology					
Structural	84 (45.41%)	36 (65.45%)	48 (36.92%)	12.692	<0.001
Other	101 (54.59%)	19 (34.55%)	82 (63.08%)		
Maternal Miscarriage History					
Yes	29 (15.68%)	10 (18.18%)	19 (14.62%)	0.372	0.542
No	156 (84.32%)	45 (81.82%)	111 (85.38%)		
Treatment Protocol					
Monotherapy	95 (51.35%)	37 (67.27%)	58 (44.62%)	7.942	0.005
Combination	90 (48.65%)	18 (32.73%)	72 (55.38%)		
Child's Age	15.00 (4.00)	14.00 (3.00)	16.00 (5.00)	3.414	<0.001
Disease Duration	7.00 (3.00)	7.00 (3.00)	6.00 (3.00)	2.193	0.028
Maternal Age	26.06±2.75	25.98±2.99	26.10±2.65	0.267	0.790
Seizure Frequency	9.00 (3.00)	9.00 (3.00)	9.00 (4.00)	1.131	0.258
DQ Score	69.00 (4.00)	67.00 (4.00)	69.00 (4.75)	5.367	<0.001
MI Score	71.00 (4.00)	72.00 (5.00)	71.00 (3.00)	1.291	0.197
Kramer Score	10.00 (2.00)	11.00 (2.00)	9.00 (3.00)	4.874	<0.001

Note: DQ: Developmental Quotient, MI: Mental Index; Attack frequency, DQ score, MI score, and Kramer scores were all pre-treatment indicators.

PSM, the baseline data of the relapse and non-relapse groups showed no significant differences in terms of gender (P=0.840), primiparity (P=0.240), mode of delivery (P=0.643), abnormal labor (P=0.946), maternal history of miscarriage (P=0.542), or disease duration (P=0.258). However, significant difference was observed in the distribution of etiology (P< 0.001), with the relapse group having a higher proportion of structural causes (65.45% vs. 36.92%). Furthermore, significantly higher proportions of patients in the relapse group received monotherapy (P=0.005), were younger at the time of treatment (P<0.001), and

Table 14. Comparison of baseline data for the relapsed children after PSM

Indicator	Total	Relapse Group (n=20)	Non-Relapse Group (n=56)	Statistical Value	*P* value
Gender					
Male	43 (56.58%)	9 (45.00%)	34 (60.71%)	1.481	0.224
Female	33 (43.42%)	11 (55.00%)	22 (39.29%)		
Primiparity					
Yes	37 (48.68%)	8 (40.00%)	29 (51.79%)	0.819	0.365
No	39 (51.32%)	12 (60.00%)	27 (48.21%)		
Mode of Delivery					
Vaginal delivery	50 (65.79%)	13 (65.00%)	37 (66.07%)	0.008	0.931
Cesarean section	26 (34.21%)	7 (35.00%)	19 (33.93%)		
Abnormal Labor					
Yes	74 (97.37%)	20 (100.00%)	54 (96.43%)	0.734	0.392
No	2 (2.63%)	0 (0.00%)	2 (3.57%)		
Etiology					
Structural	34 (44.74%)	6 (30.00%)	28 (50.00%)	2.384	0.123
Other	42 (55.26%)	14 (70.00%)	28 (50.00%)		
Maternal Miscarriage History					
Yes	13 (17.11%)	5 (25.00%)	8 (14.29%)	1.193	0.275
No	63 (82.89%)	15 (75.00%)	48 (85.71%)		
Treatment Protocol					
Monotherapy	38 (50.00%)	6 (30.00%)	32 (57.14%)	4.343	0.037
Combination	38 (50.00%)	14 (70.00%)	24 (42.86%)		
Child's Age	15.00 (4.25)	15.00 (2.25)	15.50 (5.00)	0.285	0.776
Disease Duration	6.71±1.87	7.00±2.00	6.61±1.84	-0.802	0.425
Maternal Age	26.00 (3.25)	27.00 (3.00)	26.00 (4.00)	0.524	0.600
Seizure Frequency	9.00 (2.25)	8.00 (2.25)	9.00 (2.00)	1.304	0.192
DQ Score	69.08±3.33	68.35±3.30	69.34±3.33	1.143	0.257
MI Score	70.36±3.01	70.60±3.39	70.27±2.90	-0.421	0.675
Kramer Score	9.68±2.08	10.85±1.53	9.27±2.10	-3.081	0.003

Note: DQ: Developmental Quotient, MI: Mental Index; Attack frequency, DQ score, MI score, and Kramer scores were all pre-treatment indicators.

showed significant differences in DQ scores (P<0.001) and Kramer scores (P<0.001), as shown in **Table 13**.

After PSM, the baseline data of the relapse and non-relapse groups were re-analyzed. The results showed no significant differences between the groups in gender (P=0.224), primiparity (P=0.365), mode of delivery (P=0.931), abnormal labor (P=0.392), maternal history of miscarriage (P=0.275), patient age (P=0.776), or disease duration (P=0.425). There were also no significant differences in structural etiology (P=0.123), treatment regimen (P=0.037), seizure frequency (P=0.192), or MI scores (P=0.675). However, the relapse group had significantly lower Kramer scores than the non-relapse group (P=0.003), suggesting that after PSM, the baseline differences between the two groups were reduced and some variables no longer showed significant differences, as shown in **Table 14**.

Multivariate logistic regression analysis reveals independent predictors for IESS relapse

In the pre-PSM cohort, multivariate logistic regression identified structural etiology (OR=3.12, 95% CI: 1.65-5.89, P<0.001), monotherapy (OR=2.54, 95% CI: 1.32-4.89, P=0.005), lower DQ scores (OR=0.85, 95% CI: 0.78-0.93, P<0.001), and higher Kramer scores

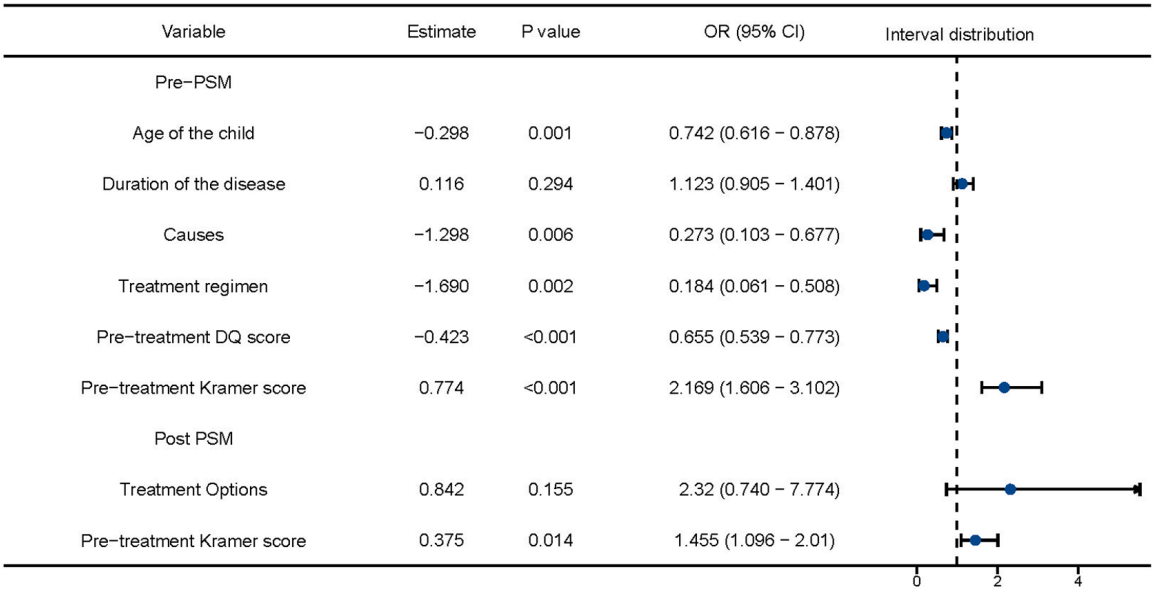

Figure 2. Multivariate Logistic regression analysis of factors associated with recurrence in IESS. Note: IESS: Infantile Epileptic Spasms Syndrome.

(OR=1.45, 95% CI: 1.22-1.72, P<0.001) as independent predictors of relapse in IESS patients ().

After PSM, only Kramer scores (OR=1.38, 95% CI: 1.11-1.71, P=0.003) remained significantly correlated with relapse. Notably, the predictive effect of treatment regimen (P=0.037) and structural etiology (P=0.123) diminished after PSM, suggesting that these factors might be influenced by other confounding variables, as shown in **Figure 2**.

EEG improvements in infantile epileptic spasms syndrome patients before and after treatment

Figure 3 displays EEG characteristics of IESS patients before and after treatment. Panel A depicts the pre-treatment EEG, where multi-focal spikes lasting longer than 1 second were observed in 50% of cases, particularly in the bilateral frontal and posterior regions, with amplitudes exceeding 300 μV. Panel B illustrates the post-treatment EEG, showing a reduction in spike frequency and amplitude, with no spikes lasting more than 1 second and the amplitudes remaining below 200 μV. Panel C demonstrates the absence of multi-focal spikes after treatment, although slow waves are still present in the posterior regions with amplitudes exceeding 200 μV. Panel D further shows the reduced presence of multi-focal spikes (lasting less than 1 second) with persistent slow waves in the posterior areas, still above 200 μV.

Discussion

IESS, a particularly challenging epileptic syndrome, evidently affects infant/toddler neurodevelopment, making treatment decisions crucial for long-term prognosis [21]. This study systematically compared ACTH combined with topiramate versus topiramate monotherapy, while also probing potential relapse risk factors. Their results suggest that combination therapy offer some advantages over monotherapy in some key indicators: spasm control, EEG improvement, and neurodevelopmental outcomes. However, the effect size remains unclear. This aligns with findings from Dozieres-Puyravel et al. [22], who argued that a steroids and vigabatrin combination was slightly more effective than sequential treatments, though their patient population wasn't exactly the same. The authors are proposing that ACTH and topiramate might even surpass the steroid/vigabatrin combination, which is a bold claim.

Topiramate, a carbonic anhydrase inhibitor, works outside the GABAergic system by interfering with sodium and calcium channels [23,

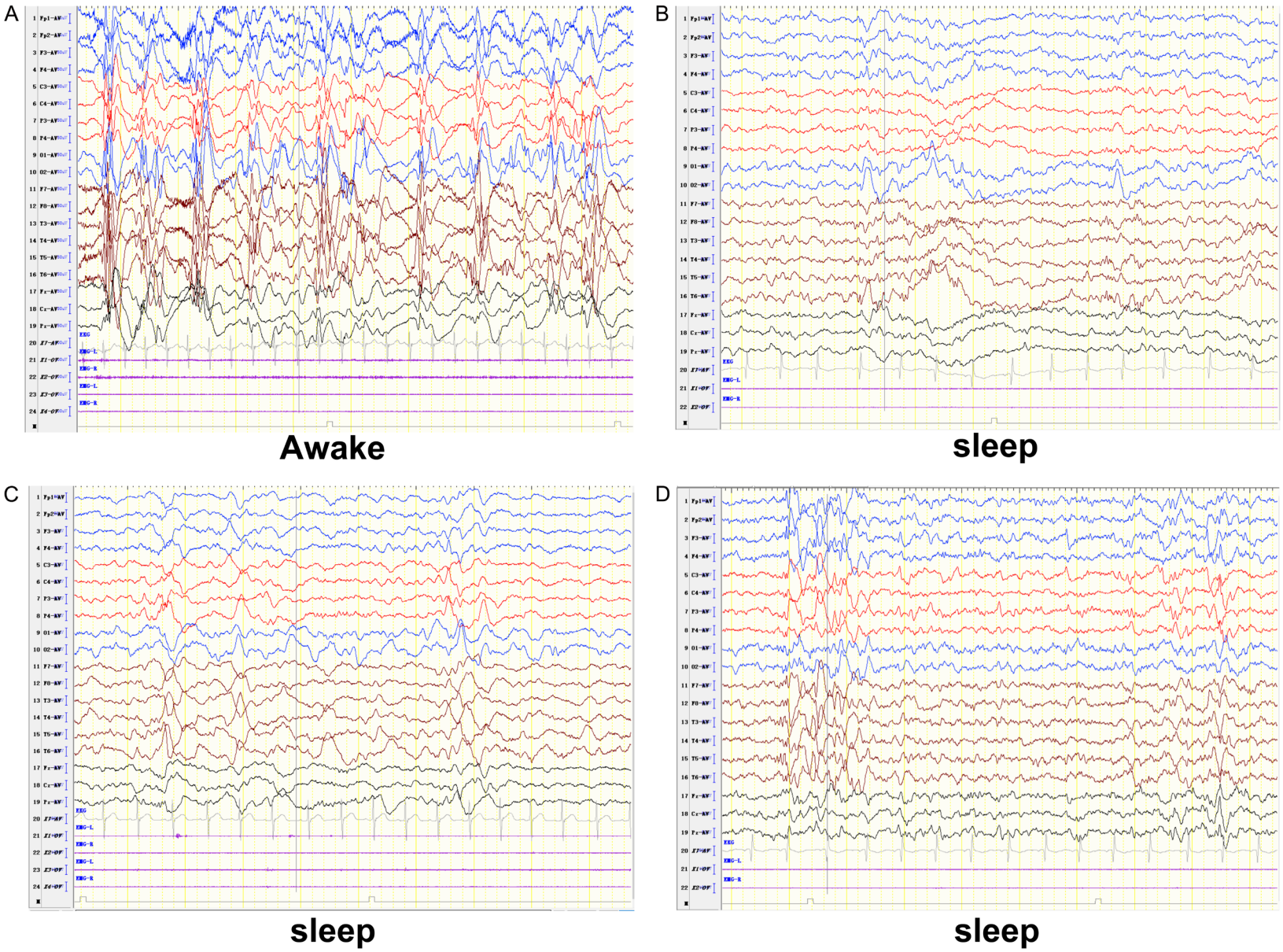
A
Awake
B
sleep
C
sleep
D
sleep

Figure 3. EEG changes before and after treatment in IESS patients. A. Pre-treatment EEG showing multi-focal spikes with durations over 1 second, and amplitudes ≥300 μV in the bilateral frontal and occipital areas. B. Post-treatment EEG showing reduced amplitude spikes (<200 μV) in the occipital region, with no multi-focal spikes lasting more than 1 second. C. Post-treatment EEG with no multi-focal spikes, but slow waves in the posterior regions exceeding 200 μV. D. Post-treatment EEG showing reduced multi-focal spikes lasting less than 1 second, with slow waves maintaining amplitudes above 200 μV in the posterior regions. Note: EEG: Electroencephalogram, IESS: Infantile Epileptic Spasms Syndrome, μV: Microvolts.

24]. On the other hand, ACTH may improve neuroinflammation and synaptic plasticity via the hypothalamic-pituitary-adrenal axis, while topiramate reduces abnormal discharges by inhibiting carbonic anhydrase and modulating ion channels. The synergy between these two mechanisms could explain the superior efficacy that the study is touting, but this is still speculative.

Regarding neurodevelopment, the combination therapy group demonstrated significantly higher DQ and MI scores and significantly lower Kramer scores compared to the control group after treatment. This aligns with findings from Zhang et al. [25], who suggested electrophysiological improvement might correlate with neurofunctional recovery via EEG complexity. These findings do provide interesting insight into the potential molecular mechanisms through which combination therapy might enhance neurodevelopment.

In terms of safety, the two groups experienced comparable adverse reactions, and those were manageable. Alammar et al. [26] reported similar findings, which is somewhat reassuring, suggesting that ACTH side effects, such as electrolyte disturbances, can be monitored and managed effectively. Additionally, Dou et al. [27] proposed that a modified Atkins diet could serve as a plan B for kids who struggle with the medication, offering a fallback option if needed.

Through multivariate analysis before and after PSM, this study identified key factors influencing relapse risk and their dynamic changes. Before PSM, structural etiology, lower DQ scores, and higher Kramer scores emerged as independent predictors of relapse, with structural etiology showing particularly high risk (HR=3.12). This result aligns with the findings of Jiang et al. [28] and Mao et al. [29], both of whom identified a high proportion of structural etiologies in IESS patients (49.4% and 42.6%, respectively) significantly associated with poorer treatment response and higher relapse rates. Notably, Mao et al. [29] further found that patients with specific abnormalities on head MRI had significantly higher relapse rates, providing more direct imaging evidence of the relationship between structural etiology and relapse risk. After PSM, Kramer scores remained a significant predictor, while the predictive effect of structural etiology weakened. This shift may reflect two important phenomena: first, Kramer scores, as a composite measure encompassing seizure frequency, EEG abnormalities, and neurological function, offering greater stability in prognostic prediction; second, the diminished predictive power of structural etiology suggests its effect may be partially mediated by other variables, such as more severe EEG abnormalities or lower baseline developmental status. Pathophysiologically, a higher Kramer score often indicates more extensive neural network abnormalities and impaired synaptic plasticity, leading to more frequent recurrence of abnormal discharges. This explains its reliability as a predictor of long-term prognosis. Overall, these findings provide crucial evidence to identify high-risk populations and inform personalized treatment strategies.

The long-term follow-up study by Kuchenbuch et al. [30] recommended continuing ACTH treatment for at least two years to reduce relapse risk. Mao et al. [29] also found that children who had used antiepileptic drugs before ACTH treatment or had developmental delays prior to spasm onset had lower short-term remission rates. These findings emphasize the necessity for more aggressive and long-term treatment for IESS children.

From a clinical practice perspective, the findings of this study have significant clinical implications. For children at high risk of relapse (e.g., structural etiology or high Kramer scores), combination therapy with ACTH and Topiramate may offer 1 superior clinical benefits compared to monotherapy. In addition to focusing on

spasm control, regular assessments of neurodevelopmental status, particularly through DQ and MI scores, are essential to monitor cognitive improvements. For children receiving combination therapy, special attention should be given to monitoring and managing electrolyte balance and other potential ACTH-related adverse reactions. These measures will help maximize treatment benefits while minimizing potential risks.

As a retrospective analysis, this study has certain limitations, including the potential for unmeasured confounding factors and reduced statistical power following propensity score matching. The relatively short follow-up period also limits long-term prognostic assessment. These methodologic constraints highlight the need for more rigorous research designs to validate the current findings. Future research should extend the follow-up period to 3-5 years to assess long-term neurodevelopmental outcomes. Multicenter prospective randomized controlled trials are also necessary to provide more reliable evidence-based guidance. Furthermore, exploring the relationship between genetic markers, neuroimaging features, and treatment response may help optimize individualized treatment strategies. Additionally, fine-tuning ACTH administration protocols and exploring other novel combination treatment modalities are worthy of further investigation to provide more comprehensive guidance for clinical practice.

Conclusion

ACTH combined with topiramate demonstrates superior efficacy compared to topiramate monotherapy in treating IESS, leading to better spasm control, EEG improvement, and neurofunctional recovery, without significantly increasing the risk of adverse reactions. Furthermore, Kramer scores were identified as the strongest independent predictor of relapse risk, further supporting their use in clinical prognostication.

Disclosure of conflict of interest

None.

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