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ORIGINAL RESEARCH

Factors Influencing the Response of Patients with Infantile Epileptic Spasms Syndrome to ACTH as Repeated First-Line Therapy

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ABSTRACT

Introduction: The treatment of infantile epileptic spasms syndrome (IESS) aims to achieve spasm control. Current first-line interventions include hormone therapy (adrenocorticotropic hormone [ACTH] and corticosteroids) and vigabatrin. Despite treatment, the response rate remains at around 40%, with some infants experiencing relapse after achieving initial spasm control. In certain cases, a second course of first-line therapy may be warranted. The objective of this study was to perform a secondary analysis of data from our previously published studies to elucidate factors influencing the efficacy of ACTH following its re-administration after the lack of response to the initial first-line treatment or relapse.

Methods: We conducted a retrospective analysis of clinical data from children with IESS who had experienced treatment failure or relapse following initial first-line therapy and who subsequently received ACTH at our institution as a second first-line treatment. We examined such variables as etiological classification, interval between treatments, age at first epileptic seizure, radiological findings, and changes in pharmacological treatment modalities, with the overall aim to assess the impact of these variables on the short-term response (disappearance of spasms for >4 weeks and without hypsarrhythmia pattern) to the second administration of the first-line therapy.

Results: Among the 128 patients with IESS identified and included in the analysis, 50 (39.1%) achieved a short-term response. Comparative analysis indicated that responders had a shorter duration between the initial first-line therapy and the initiation of the second first-line treatment (median 1.00 [interquartile range {IQR} 0.00, 2.00] vs. 1.75 [IQR 0.50, 3.88] months), were younger at the time of the second first-line treatment (median 11 [IQR 8, 17] vs. 16 [IQR 10, 24] months, $p=0.008$), and were less likely to present with additional seizure types during spasm episodes (12.0% vs. 28.2%,

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$p=0.030$). A multifactorial regression model indicated that older age at first seizure and a short-term response to initial first-line treatment were associated with a higher likelihood of obtaining an initial response in the subsequent ACTH treatment (odds ratio [OR] 2.69, 95% confidence interval [CI] 1.39, 7.23, $p=0.014$ and OR 5.41, 95% CI 1.48, 23.90, $p=0.016$, respectively). Conversely, an older age at the time of the initial first-line treatment, an older age at the onset of epileptic spasms, and patients with congenital structural abnormalities without genetic abnormalities were less likely to achieve an initial response in subsequent ACTH treatment (OR 0.85, 95% CI 0.78, 0.92, $p<0.001$; OR 0.43, 95% CI 0.16, 0.82, $p=0.032$; and OR 0.18, 95% CI 0.04, 0.69, $p=0.016$, respectively)..

Conclusion: A second ACTH therapy regimen (second first-line treatment) may help some children with IESS who did not respond to the initial treatment or who subsequently relapsed, with one-third of patients responding in the short-term. Congenital anomalies without genetic abnormalities and older spasm onset age lessen the odds of response, while younger age at ACTH re-treatment could improve these. ACTH may be reconsidered after initial treatment response followed by relapse.

Keywords: Infantile epileptic spasms syndrome; First-line therapy; Adrenocorticotropic hormone; Second treatment; Initial response

Key Summary Points

Why carry out this study?

The treatment options for infantile epileptic spasms syndrome (IESS) are limited, and it remains unclear which patients may benefit from a second course of adrenocorticotropic hormone (ACTH) treatment (second first-line treatment)

The aim of this study was to explore the effectiveness of using ACTH as a second first-line treatment and the relevant factors associated with response

What was learned from the study?

Over one-third of patients with IESS achieved a short-term response following the second course of ACTH treatment; however, patients with congenital structural anomalies without genetic alterations may not be suitable for this treatment option

For some patients with IESS, ACTH can be used as a repeated first-line treatment option before attempting another therapy, such as surgery

INTRODUCTION

Infantile epileptic spasms syndrome (IESS) is an epilepsy syndrome characterized by infantile onset and epileptic spasms [1, 2]. The current treatment for children with IESS aims to effectively control the spasms [2]. Previous studies showed that long-term control of spasms is associated with the neurodevelopmental outcomes of children with IESS [2–4]. The first-line treatment recommended by the International League Against Epilepsy (ILAE) for IESS includes steroids (adrenocorticotropic hormone [ACTH] and oral corticosteroids) and vigabatrin (VGB) [2]. The short-term response rate of children with IESS to first-line treatment is approximately 40% [5, 6], with some children subsequently experiencing relapses [6, 7]. These children may undergo

first-line treatment again (repeated first-line treatment) in an attempt to achieve spasm control [8]. Current research suggests that the concurrent use of steroid drugs and VGB may increase the short-term control rate of children with IESS [9–11]. However, the promotion of combination therapy worldwide still faces challenges, especially in the context of ongoing issues with unequal distribution of medical resources, considering the economic cost, availability of drugs, and potential safety risks of their concomitant use (severe VGB-related encephalopathy and even death [12]).

Approximately one-third of patients failing first-line treatment may respond to second-line treatment options, particularly when mechanisms of the latter differ from initial therapies [8]. Notably, ACTH shows efficacy in IESS treatment even after VGB failure [13], suggesting potential benefits of sequential first-line retreatment. However, predictors of second-line success remain unclear. Etiology is a critical prognostic factor, with genetic and congenital structural anomalies correlating with poorer outcomes [14–17]. Advances in genetic testing now enable definitive etiological diagnosis in approximately three quarters of IESS cases [5, 17], reducing historical uncertainties [18–20].

In the study reported here, we examined 577 patients with IESS in whom exhaustive clinical examinations were conducted to determine the underlying causes of the syndrome [5]. Building upon this dataset, we aimed to observe the efficacy of the repeated first-line treatment following no response to the initial first-line treatment or subsequent relapse. We further hypothesized that a subset of patients with IESS who experienced no response to initial treatment or subsequent relapse, characterized by specific etiological factors or clinical features, such as short-term response followed by relapse, might have a higher likelihood of achieving seizure-free outcomes with a second ACTH treatment. This study was designed to explore the potential association between specific etiological factors or clinical characteristics and treatment outcomes in patients with IESS, particularly in the context of repeated first-line treatment.

METHODS

Participants

The focus of this study was a cohort of children with IESS who had sought medical care at the People's Liberation Army General Hospital in Beijing, China, from January 2018 to June 2023 and who had undergone clinical examinations to determine the underlying cause of their condition. Inclusion criteria included (1) meeting the diagnostic criteria for IESS as per the 2022 ILAE guidelines [2]; (2) presence of spasms confirmed by electroencephalography (EEG) at the hospital visit; (3) previous unsuccessful or relapsed standardized first-line treatment at external institutions, including standardized treatment involving the administration of an adequate dose of ACTH (2.5 U/kg/day) for longer than 2 weeks [5], VGB at a minimum dose equivalent to the recommended dose (50–150 mg/kg/day), or oral steroids at the prescribed dose (2 mg/kg/day) for 1 month, with a gradual tapering off after the initial 2 weeks [14]; (4) completion of a 14-day natural ACTH infusion treatment at the People's Liberation Army General Hospital (2.5 U/kg/day; Shanghai No.1 Biochemical & Pharmaceutical Co. Ltd., Shanghai, China) for 2 weeks as second first-line treatment (SFT). Exclusion criteria were: (1) children who had previously received ≥ 2 different first-line treatments with distinct mechanisms of action (ACTH/oral steroids and VGB). A description of the detailed process of including participants in the study shown in Fig. 1.

Ethical approval for the study was granted by the Ethics Committee of the First Medical Centre of the PLA General Hospital (S2020-337-01). This study uses data from our previous study [5] checked by a statistician. The study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments.

Data Collection

Clinical Data

The clinical data collected included gender, age at seizure onset, whether seizure was

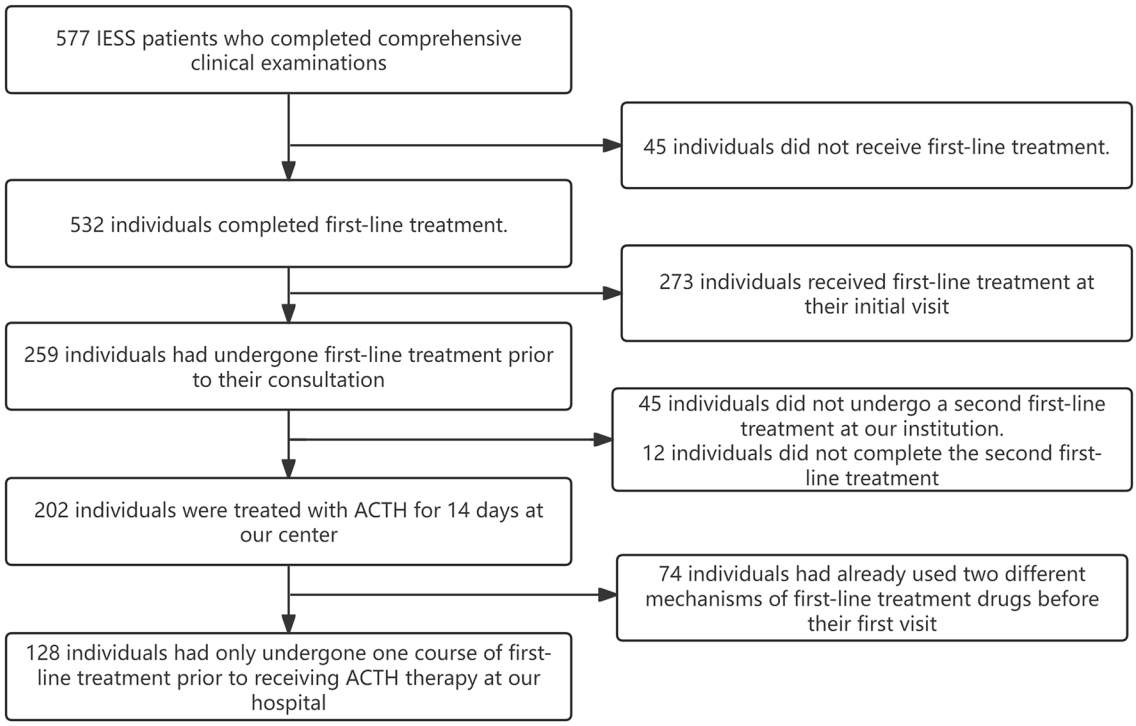

Fig. 1 Flowchart of study participants. *ACTH* adrenocorticotropic hormone, *IESS* infantile epileptic spasms syndrome

early-onset (seizure onset at age ≤ 3 months), whether the first seizure onset presented as epileptic spasm (ES), age at ES onset, whether ES was late-onset (ES onset at the age > 12 months and ≤ 24 months), whether other seizure types manifested during ES, whether hypsarrhythmia was present, whether there was any developmental delay before ES onset, age of previous first-line treatment (PFT; before the visit to our center), lead time of PFT (length of time between ES onset and PFT), PFT medication (ACTH, VGB, or oral steroids), PFT effect (response or no response), age of SFT in our center, whether the mechanism changed in the SFT (such as those patients who had PFT with VGB), and length of time between PFT and SFT.

Determination of Abnormal Magnetic Resonance Imaging Findings

Magnetic resonance imaging (MRI) findings regarding IESS include three major categories (MRI types) and seven subcategories (MRI subtypes) [5]. The first major category includes acquired structural abnormalities, including the subtype perinatal acquired brain injury (such as hypoglycemic encephalopathy, hypoxic-ischemic encephalopathy, prematurity-related brain injury, or other early life factors that lead to periventricular leukomalacia or intraventricular hemorrhage) and the subtype postnatal acquired brain injury (includes infantile brain injuries caused by infection, stroke, or other factors during postnatal development). The second major category comprises congenital structural abnormalities, and includes the subtype malformations of cortical development (MCD, such as focal cortical dysplasia, polymicrogyria, schizencephaly, and hemimegalencephaly) [21], the subtype diffuse brain diseases [22] (DBD; including developmental abnormalities affecting multiple structures or cell lineages with a broad spatial distribution), the subtype developmental tumors (such as tuberous sclerosis and neuroglioma), and the subtype volume loss (only considered to be etiological if a definitive pathogenic gene is identified [17]; these cases considered to be

due to atrophy caused by hormone treatment are not regarded as volume loss). If none of the above-mentioned abnormalities are identified, the case is classified as the third major category: normal [5]. If a patient was previously been determined to be normal by a radiologist, this categorization still needed reconfirmation by a pediatric neurologist; in cases of disagreement, the images were reviewed again, followed by the final decision by the radiologist.

Etiological Classification

All patients were classified using our previous classification method (IESS classification [5]: clinical assessment, cranial MRI results, genetic testing, and metabolic testing) into five categories: congenital structural abnormalities with positive genetic findings; congenital structural abnormalities without positive genetic findings; unknown, acquired structural abnormalities; and normal structure with positive genetic findings. These MRI classification of the MRI findings and IESS etiological classification are shown in Fig. 2).

Second First-Line Treatment

The treatment regimen for all patients undergoing SFT with ACTH consisted of intravenous infusion of natural ACTH (2.5 U/kg/day; Shanghai No.1 Biochemical & Pharmaceutical Co. Ltd.) for 2 weeks.

Definition of the Initial Response

The initial response for both PFT and SFT was defined into two categories: responders and non-responders. The definition of a responder was consistent with our previous studies, in which a short-term response was defined as the disappearance of spasms for > 4 weeks. Otherwise, it was considered a non-response [5]. After completing the SFT, each patient underwent an EEG examination lasting 2–4 h to assess whether

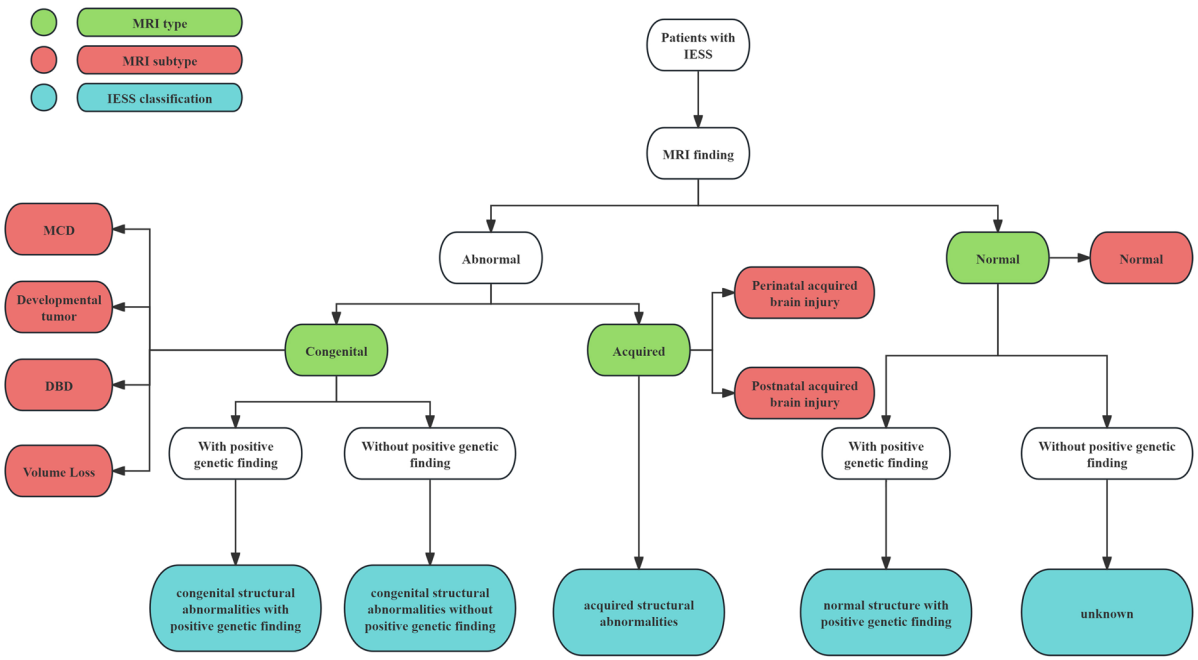

Fig. 2 Flowchart of MRI classification and etiological classification (IESS classification). *MCD* Malformations of cortical development, *DBD* developmental brain disorders, *IESS* infantile epileptic spasms syndrome, *MRI* magnetic resonance imaging

there was a response or not, which included at least one cycle from wakefulness to sleep and back to wakefulness.

Statistical Analysis

The primary objective of this study was to identify demographic or clinical differences among patients who underwent repeated first-line treatment. Therefore, we compared the differences in the above-mentioned observation indicators between responder and non-responder groups receiving SFT. For categorical variables, chi-square or Fisher's exact test was used. Depending on the results of the normality test, either the independent samples t-test or the Mann–Whitney U-test was used for continuous variables. We performed a univariate logistic regression test for each variable to further explore the influence of the above-mentioned variables on the response to SFT. Subsequently, a multivariate logistic regression model was established using a bidirectional stepwise method. The variables included in the multivariate logistic regression model were selected based on the minimum Akaike information criterion (AIC) value after the inclusion of the above-listed factors into the model. All analyses were performed using R ® Foundation for statistical computing, Vienna, Austria).

RESULTS

A total of 128 patients with IESS with first-line treatment failure or subsequent relapse after first-line treatment at other institutions visited our center for a second administration of the first-line treatment regimen with ACTH. Following the SFT with ACT, 50 children (39.1%) achieved a short-term response. Table 1 presents the key demographic and clinical features of the study population. Among the 128 participants, 44.5% were female and 55.5% were male, with no significant differences between SFT responders and non-responders ($p=0.527$). The median (interquartile range [IQR]) ages of SFT responders and non-responders at seizure and spasm onset were 5.0 (IQR 3.0, 7.0) and 5.0 (IQR 3.4, 7.5) months, respectively; there was no statistically significant difference between the groups ($p=0.611$ and 0.872). Most participants experienced seizure onset after 3 months (77.3%) and spasm onset within the first 12 months (89.1%); in 78.1% the first seizure manifested as spasm (78.1%); PFT response (26.0% vs. 16.7%) and hypsarrhythmia occurred during spasm onset (74.2%); there were no significant differences between SFT responders and non-responders ($p=0.887$, 0.394, 0.396, 0.200, and 0.434 respectively). A total of 78.1% of patients did not have other seizure types during spasms, but there were fewer patients in the response group with other seizure types during spasms than in the non-response group (12.0% vs. 28.2%, $p=0.030$). PFT factors (median [IQR] in the SFT response and non-response groups, such as age (median 7.0, [4.5, 9.4] vs. 8.0 [5.5, 12.0] months) and specific treatment options (ACTH, VGB, and oral corticosteroids: 46.0%, 34.0%, and 20.0% vs. 44.9%, 32.1%, and 23.1%, respectively), were not significantly different ($p=0.099$ and 0.916, respectively). However, the response group had a shorter PFT lead time (1.00 [0.00, 2.00] vs. 1.75 [0.50, 3.88] months), $p=-0.03$). For the SFT, factors such as treatment mechanism change (34.0% vs. 32.1%) and lead time between PFT and SFT (3 [2, 6] vs. 5 [2, 13] months) were not significantly different between the response and non-response groups ($p=0.819$ and 0.148, respectively). However, participants in the response group were younger during SFT (11 [8, 17] vs. 16 [10, 24] months, $p=0.008$). MRI and subtype findings were not significantly different between the groups ($p=0.369$ and 0.415). After classifying the etiology, no significant differences were observed between the two groups ($p=0.067$).

In the univariate logistic regression, having other seizure types during spasms, PFT age, SFT age, and etiology of congenital structural abnormalities without positive genetic findings (compared to unknown causes) reduced the probability of SFT response (odds ratio [OR] 0.35, 95% confidence interval [CI] 0.12, 0.88, $p=0.035$; OR=0.92, 95% CI 0.84, 0.99, $p=0.039$; OR=0.41, 95% CI 0.94, 0.90, 0.98, $p=0.008$; OR=0.22, 95% CI 0.06, 0.73, $p=0.019$) (Table 2).

Table 1 Patient demographics and baseline characteristics between responders and non-responders in children with infantile epileptic spasms syndrome treated with adrenocorticotropic hormone as repeated first-line therapy

Patient characteristics and collected data		SFT responders ($N = 50$)	SFT non-responders ($N = 78$)	Statistical value	p value
Clinical characteristics ($N = 128$ patients)	Overall values				
Gender				0.40	0.527[a]
- Female	57 (44.5%)	24 (48.0%)	33 (42.3%)		
- Male	71 (55.5%)	26 (52.0%)	45 (57.7%)		
Age of seizure onset (months)	5.0 [3.0, 7.0]	5.0 [3.1, 7.0]	5.0 [3.0, 6.9]	2,054.50	0.611[b]
Seizure early-onset	29 (22.7%)	11 (22.0%)	18 (23.1%)	0.02	0.887[a]
First seizure onset presenting as epileptic spasms	100 (78.1%)	41 (82.0%)	59 (75.6%)	0.72	0.396[a]
Age of epileptic spasm onset (months)	5.0 [3.4, 7.5]	5.0 [3.5, 7.0]	5.3 [3.0, 8.0]	1,916.50	0.872[b]
Epileptic spasm late-onset	14 (10.9%)	4 (8.0%)	10 (12.8%)	0.73	0.394[a]
With other seizure types during epileptic spasm	28 (21.9%)	6 (12.0%)	22 (28.2%)	4.68	0.030[a]
Hypsarrhythmia	95 (74.2%)	39 (78.0%)	56 (71.8%)	0.61	0.434[a]
Developmental delay before epileptic spasm onset	60 (47.2%)	22 (44.9%)	38 (48.7%)	0.18	0.675[a]
Age at PFT (months)	7.3 [5.4, 10.6]	7.0 [4.5, 9.4]	8.0 [5.5, 12.0]	1,612.00	0.099[b]
Lead time of PFT (months)	1.50 [0.50, 3.00]	1.00 [0.00, 2.00]	1.75 [0.50, 3.88]	1,518.50	0.034[b]
PFT medication				0.18	0.916[a]
- ACTH	58 (45.3%)	23 (46.0%)	35 (44.9%)		
- VGB	42 (32.8%)	17 (34.0%)	25 (32.1%)		
Oral steroids	28 (21.9%)	10 (20.0%)	18 (23.1%)		
PFT responder	26 (20.3%)	13 (26.0%)	13 (16.7%)	1.64	0.200[a]
Age at SFT months	13 (9, 21)	11 (8, 17)	16 (10, 24)	1,403.00	0.008[b]
Mechanism changed in SFT	42 (32.8%)	17 (34.0%)	25 (32.1%)	0.05	0.819[a]
Elapsed time between PFT and SFT (months)	4 (2, 10)	3 (2, 6)	5 (2, 13)	1,654.00	0.148[b]
MRI type				3.10	0.212[a]
- Normal	47 (36.7%)	20 (40.0%)	27 (34.6%)		
- Congenital	50 (39.1%)	15 (30.0%)	35 (44.9%)		
- Acquired	31 (24.2%)	15 (30.0%)	16 (20.5%)		
MRI subtype					0.415[c]

Table 1 continued

Patient characteristics and collected data		SFT responders ($N=50$)	SFT non-responders ($N=78$)	Statistical value	p value
Clinical characteristics ($N=128$ patients)	**Overall values**				
- Normal	47 (36.7%)	20 (40.0%)	27 (34.6%)		
- Volume loss	5 (3.9%)	3 (6.0%)	2 (2.6%)		
- Developmental tumor	8 (6.3%)	3 (6.0%)	5 (6.4%)		
- DBD	19 (14.8%)	5 (10.0%)	14 (17.9%)		
- Perinatal acquired brain injury	20 (15.6%)	9 (18.0%)	11 (14.1%)		
- Postnatal acquired brain injury	11 (8.6%)	6 (12.0%)	5 (6.4%)		
- MCD	18 (14.1%)	4 (8.0%)	14 (17.9%)		
IESS classification					0.067[c]
- Unknown	37 (28.9%)	18 (36.0%)	19 (24.4%)		
- Congenital structural abnormalities with positive genetic finding	27 (21.1%)	11 (22.0%)	16 (20.5%)		
- Acquired structural abnormalities	31 (24.2%)	15 (30.0%)	16 (20.5%)		
- Normal structure with positive genetic finding	10 (7.8%)	2 (4.0%)	8 (10.3%)		
- Congenital structural abnormalities without positive genetic finding	23 (18.0%)	4 (8.0%)	19 (24.4%)		

Values in table are presented as the number of patients (N) with the percentage in parentheses or as the median with the interquartile range in square brackets

DBD Diffuse brain diseases, *IESS* infantile epileptic spasms syndrome, *MCD* malformations of cortical development, *PFT* previous first-line treatment, *SFT* second first-line treatment

[a]Pearson's chi-squared test

[b]Wilcoxon rank sum test

[c]Fisher's exact test

In the subsequent multivariate regression model, the model constructed using first seizure type, age at seizure onset, age at spasm onset, other type(s) during spasm, hypsarrhythmia, PFT effect, age at SFT, and IESS classification had the lowest AIC (152.427). Therefore, these eight factors were analyzed using a multivariate regression model. The final results showed that patients with an older age at seizure onset and PFT response had a higher probability of achieving a short-term response after failing the first-line treatment with ACTH (OR 2.69, 95% CI 1.39, 7.23, $p=0.014$; OR = 5.41, 95% CI 1.48, 23.90, $p=0.016$). However, older age at SFT, age at spasm onset, and etiology of congenital structural abnormalities without positive genetic findings were associated with a lower probability of achieving a short-term response (OR 0.85, 95% CI 0.78, 0.92, $p<0.001$; OR 0.43, 95% CI

Table 2 Univariate logistic regression model for factors associated with response to repeated first-line treatment with adrenocorticotropic hormone in children with infantile epileptic spasms syndrome

Characteristic	Odds ratio	95% Confidence interval	*p* value
Gender	0.79	0.39, 1.62	0.528
Age of seizure onset	0.99	0.90, 1.07	0.717
Seizure early-onset	0.94	0.39, 2.18	0.887
First seizure onset presents as epileptic spasms	1.47	0.60, 3.56	0.397
Age of epileptic spasm onset	0.96	0.88, 1.04	0.345
Epileptic spasm late-onset	0.59	0.15, 1.89	0.398
Other seizure types during epileptic spasm	0.35	0.12, 0.88	0.035
Hypsarrhythmia	1.39	0.61, 3.20	0.435
Development delay before epileptic spasm onset	0.86	0.42, 1.76	0.675
Age of PFT	0.92	0.84, 0.99	0.039
Lead time of PFT	0.86	0.73, 0.98	0.053
PFT medication			
- ACTH	–	–	
- VGB	1.03	0.46, 2.33	0.934
- Oral steroids	0.85	0.32, 2.13	0.725
PFT responders	1.76	0.74, 4.19	0.203
Age at SFT (months)	0.94	0.90, 0.98	**0.008**
Mechanism changed in SFT	1.09	0.51, 2.32	0.819
Length of time between PFT and SFT	0.95	0.90, 1.00	0.081
MRI type			
- Normal	–	–	
- Congenital	0.58	0.25, 1.34	0.200
- Acquired	1.27	0.51, 3.15	0.612
MRI subtype			
- Normal	–	–	
- Volume loss	2.03	0.31, 16.48	0.462
- Developmental tumor	0.81	0.15, 3.70	0.789
- DBD	0.48	0.14, 1.49	0.223
- Perinatal acquired brain injury	1.1	0.38, 3.18	0.853
- Postnatal acquired brain injury	1.62	0.43, 6.35	0.474

Table 2 continued

Characteristic	Odds ratio	95% Confidence interval	*p* value
- MCD	0.39	0.10, 1.26	0.136
IESS classification			
- Unknown	–	–	
- Congenital structural abnormalities with positive genetic finding	0.73	0.26, 1.97	0.531
- Acquired structural abnormalities	0.99	0.38, 2.58	0.983
- Normal structure with positive genetic finding	0.26	0.04, 1.23	0.12
- Congenital structural abnormalities without positive genetic finding	0.22	0.06, 0.73	**0.019**

DBD diffuse brain diseases, *IESS* infantile epileptic spasms syndrome, *MCD* malformations of cortical development, *MRI* magnetic resonance imaging, *PFT* previous first-line treatment, *SFT* second first-line treatment

Table 3 Multivariate logistic regression model for factors associated with response to repeated first-line adrenocorticotropic hormone treatment in children with infantile epileptic spasms syndrome

Characteristic	OR1	95% CI	*p* value[a]
Age of seizure onset	2.69	1.39, 7.23	0.014
First seizure onset presents as epileptic spasms	0.36	0.09, 1.44	0.148
Age of epileptic spasm onset	0.43	0.16, 0.82	0.032
Other types during epileptic spasm	0.45	0.15, 1.39	0.166
Hypsarrhythmia	2.08	0.75, 5.73	0.159
PFT response	5.41	1.48, 23.90	0.016
SFT age	0.85	0.78, 0.92	< 0.001
IESS classification			
- Unknown	–	–	
- Congenital structural abnormalities with positive genetic finding	1.17	0.35, 3.95	0.803
- Acquired structural abnormalities	3.09	0.92, 11.40	0.076
- Normal structure with positive genetic finding	0.23	0.02, 1.45	0.148
- Congenital structural abnormalities without positive genetic finding	0.18	0.04, 0.69	0.016

CI Confidence interval, *DBD* diffuse brain diseases, *IESS* infantile epileptic spasms syndrome, *PFT* previous first-line treatment, OR odds ratio, *SFT* second first-line treatment, *MCD* malformations of cortical development

[a]Underlined values: patients with an older age at seizure onset and PFT response had a higher probability of achieving a short-term response after failing the first-line treatment with ACTH ($p = 0.014$ and $p = 0.016$, respectively. Older age at SFT, age at spasm onset, and etiology of congenital structural abnormalities without positive genetic findings were associated with a lower probability of achieving a short-term response ($p < 0.001$, $p = 0.032$, and $p = 0.016$, respectively

0.16, 0.82, $p=0.032$; OR0.18, 95% CI 0.04, 0.69, $p=0.016$) (see Table 3).

Taking into consideration that all patients underwent MRI and that the MRI results were significantly associated with etiological classification, we analyzed the correlation between MRI results and etiological classification. The results revealed that there was a significant correlation between the MRI results and etiological classification (contingency coefficient = 0.839, Cramer's $V=0.769$, $p<0.001$). Patients classified with congenital structural abnormalities without positive genetic findings were all categorized as having either MCD (14 patients) or DBD (9 patients) (Table 4).

DISCUSSION

The treatment of IESS is currently challenging [23, 24]. First-line medications typically include ACTH and VGB, but not all patients respond to these treatments [3, 25, 26]. In addition to pharmacotherapy, other treatments, such as vagus nerve stimulation and surgery, may be effective

Table 4 Association analysis between infantile epileptic spasms syndrome classification and magnetic resonance imaging subtypes

MRI subtypes	IESS classification					Total
	Acquired structural abnormalities	Congenital structural abnormalities with positive genetic finding	Congenital structural abnormalities without positive genetic finding	Normal structure with positive genetic finding	Unknown	
MRI subtype						
- DBD	0	10	9	0	0	19
- Developmental tumor	0	8	0	0	0	8
- MCD	0	4	14	0	0	18
- Normal	0	0	0	10	37	47
- Perinatal acquired brain injury	20	0	0	0	0	20
- Postnatal acquired brain injury	11	0	0	0	0	11
- Volume loss	0	5	0	0	0	5
Total	31	27	23	10	37	128
Contingency coefficient = 0.8385097		Cramer's $V=0.7694348$			$p<0.001$	

Values in table are presented as the number of patients

DBD diffuse brain diseases, *IESS* infantile epileptic spasms syndrome, *MCD* malformations of cortical development, *MRI* magnetic resonance imaging

in some cases, but their availability varies by region and healthcare system [24, 27, 28]. Therefore, opting to try first-line medications a second time might be an option for patients did not respond to the initial treatment or who subsequently relapsed. Knupp et al. [8] reported that the response rate of patients with IESS undergoing repeated first-line treatment after failure to respond to the initial first-line treatment was 37.2% in their study [8]. In our study, the effectiveness of the second attempt with the first-line treatment was 39.1%, which is similar to the results of Knupp et al. [8]. Thus, even after first-line treatment failure or relapse, a reconsideration of ACTH or other first-line medications might still be a treatment option for some patients.

Riikonen et al. [29] showed that 74% (14/19) of patients with IESS who responded to the first ACTH treatment experienced a short-term response during a second ACTH therapy, whereas only 23% (3/13) of those who did not respond to the initial treatment showed a response during the second round of ACTH therapy. These results suggest that patients who respond to the initial first-line therapy are more likely to respond to a second ACTH treatment [29]. Although the proportion of patients who responded to ACTH as a second first-line therapy in our study was lower than that reported by Riikonen et al. [29], we noted that in the latter's study, 33 patients with IESS relapsed after a short-term response and only 19 underwent a second ACTH therapy, which was administered immediately after relapse. In our study, however, those relapsed patients only received a second ACTH treatment as a first-line therapy after a period of time had elapsed since their relapse and they had presented to our center. This may be a reason for the difference in outcomes between our study and that of Riikonen et al. [29]. Nonetheless, the findings of both Riikonen et al. [29] and the present study indicate that patients who respond to an initial first-line therapy are more likely to achieve a short-term response when ACTH is used as a second first-line treatment.

In the present study, a multifactorial model confirmed that patients with congenital structural abnormalities without genetic anomalies had a lower probability of achieving treatment response. Additionally, all patients with this etiology had either MCD or DBD. Although there was no statistical difference in the proportion of MCD and DBD between the response and no-response groups, the actual proportion of patients with MCD and DBD was higher in the no-response group than in the response group. At the same time, patients with MCD and DBD also accounted for a very high proportion in another etiological category: congenital structural abnormalities combined with genetic anomalies. However, this category did not impact short-term efficacy in the multifactorial model. The reason for this conclusion may be related to the fact that some patients with volume loss combined with genetic anomalies were categorized, whereas volume loss is not as clearly associated with epilepsy as MCD or DBD [22].

Therefore, our study indicates that patients with MCD or DBD might not be suitable for further ACTH treatment after failure to respond to the initial first-line therapy. This conclusion is similar to the conclusions drawn from the authors of previous studies suggesting that patients with congenital structural abnormalities often have intractable epilepsy, with surgery being a better option [30–32]. The ILAE consensus also clearly states that referral to surgery for epilepsy surgical evaluation should be made as early as possible when structural abnormalities are present [33, 34]. The results of our study support this strategy. Given the economic and time costs of undergoing a second first-line treatment, early pre-surgical assessment of patients with congenital structural abnormalities may reduce unnecessary medical procedures.

Our results also showed that the older the age at the onset of the first epileptic seizure, the higher the likelihood of obtaining a short-term response to repeated first-line treatment. The latest classification of epilepsy syndromes by the ILAE emphasizes early infantile developmental encephalopathy epilepsy (EIDEE), a syndrome that includes previously recognized Ohtahara syndrome and early myoclonic encephalopathy [2]. Seizures in this syndrome are typically difficult to control and may evolve into IESS, with the affected children possibly having a lower response rate to first-line treatment [2]. Also, our

previous research indicated that when the first epileptic seizure occurs within the first 3 months of age, the probability of responding to first-line treatment is reduced [5]. Therefore, the relationship between age at seizure onset and the efficacy of repeated first-line treatment in the current study may be explained by the presence of children who have transitioned from EIDEE. Moreover, the older the age at spasm onset, the less likely the short-term response to ACTH treatment after having no response to the initial first-line treatment or relapse. Past studies have shown that children with late-onset spasms are less likely to achieve a short-term response [35, 36], which is consistent with our study results.

In the present study, we found that the older the age at the second attempt of first-line treatment, the lower the probability of achieving a short-term response. In a previous intergroup analysis, we found that although the lead time to PFT or between PFT and SFT did not show intergroup differences, they both exhibited a trend towards a difference. For example, the median lead time of PFT in the response group was 1 month, in contrast to 1.25 months in the non-response group. The median lead time between PFT and SFT was 3 months in the response group and 5 months in the non-response group. However, there were no significant differences between the two groups in terms of the age at seizure onset or the age at spasm onset. Since the age of SFT is based on the sum of the above-mentioned time points, it was correlated with efficacy in the final multifactorial regression model due to the reasons mentioned above.

Previous research indicated that the early inset of first-line treatment may be an important factor towards achieving a short-term response among patients undergoing first-line treatment for the first time [5, 9]. Knupp et al. suggested that proceeding to the second treatment as soon as possible after failure of the first-line treatment may be a favorable factor in obtaining a short-term response to the second treatment [8]. Our study results also imply that repetition the first-line treatment should be pursued promptly after the absence of response to the initial first-line treatment or relapse is determined.

Early research by Granström et al. suggested that switching to a second treatment with a different mechanism as the first-line treatment may benefit children with IESS [37]. The study population of these authors consisted of 21 children with IESS who were unresponsive to initial treatment with VGB and subsequently were given ACTH, of whom 11 (52.3%) achieved a response [37]. In the study of Knupp et al. [8], switching to a first-line treatment drug with a different mechanism appeared to facilitate a response in the second round of treatment. However, our study did not replicate this finding. We noted that in Knupp et al.'s research [8], 56% of patients received ACTH/oral steroid for their second treatment, while in our study, only 32% of patients experienced a change in the mechanism of their treatment when using ACTH for the second time. We hypothesize that the discrepancy between our results and those of Knupp et al. may be due to this difference. Consequently, further research is needed to confirm whether switching to a first-line drug with a different mechanism of action, particularly ACTH, as a second treatment, leads to an easier short-term response in the second treatment.

We found that another factor possibly affecting the efficacy of SFT was the effectiveness of the first first-line treatment attempt, which might be more straightforward to understand. After all, patients who achieve a short-term response to the initial first-line treatment are more likely to be inherently more sensitive to the first-line treatment or relatively more likely to achieve a short-term response.

Limitations

There are a number of limitations to our study. First, this it is a retrospective study. Thus, all data were based on research previously published by our group. Many patients were excluded due to the nature of the research, which may introduce a certain bias in the results. Second, although our results suggest that patients with certain etiologies may not be suitable candidates for ACTH treatment after showing no response to the initial first-line treatment or subsequent relapse,

in the etiological classification we could find no definitive cause for about 28.9% of patients. Considering that the exploration of etiologies is still not sufficiently comprehensive, the interpretation of this result should be cautious. As the sample size expands and the etiologies become further clarified, the above results may change. However, considering the current clinical diagnostic tools available, this proportion is already very close to the percentage of unknown causes reported in the past two studies. Therefore, our results should be treated with caution. This study did not include an evaluation of side effects, given the lower incidence of side effects associated with natural ACTH. Considering that the number of patients with genetic mutations in this study was not large, and there was a wide variety of relevant genes, resulting in a small number of patients for each specific mutation type, this study did not analyze for correlations between specific genetic mutation subtypes and better ACTH response. Finally, this study did not include a statistical analysis of the long-term follow-up of patients, as this work is still ongoing. Future research will present these findings.

CONCLUSION

Our study found that even after the failure of the initial first-line treatment, attempting ACTH treatment again may still be worthwhile for some children with IESS, with over one-third of patients achieving a short-term response. However, those patients with congenital structural abnormalities without genetic anomalies may not be suitable for further ACTH treatment. The older the child at the spasm onset, the lower the likelihood of achieving a short-term response. Additionally, the older the child at seizure onset and the younger the child at the second ACTH treatment, the higher the likelihood of obtaining a short-term response. ACTH treatment could also be considered if there was a short-term response to the initial first-line treatment but subsequent relapse. Certainly, before initiating a second treatment, it is crucial to thoroughly collect available clinical data and consider the factors mentioned above to assess the appropriateness of using ACTH for treatment again.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. No financial or non-financial benefits have been received or will be received from any party related directly or

indirectly to the subject of this article by all authors (Wenrong Ge, Ping Pang, Ziyan Zhang, Lin Wan and Guang Yang). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Ethical Approval. Ethical approval for the study was granted by the Ethics Committee of the First Medical Centre of the PLA General Hospital (S2020-337-01). This study uses data from our previous study [5] checked by a statistician. The study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments.

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