

The response to ACTH is determined early in the treatment of infantile spasms

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ABSTRACT – Although adrenocorticotrophic hormone is the most commonly used treatment for infantile spasms in the United States, the optimal regimen for this indication is not known. The purpose of this study was to elucidate the optimal adrenocorticotrophic hormone treatment duration. We conducted a retrospective chart review of response to adrenocorticotrophic hormone among all patients with infantile spasms managed at our institution from January 2009 to September 2013. Treatment response was defined as clinical remission for greater than or equal to 28 days starting at any point within the adrenocorticotrophic hormone course and remission of hypsarrhythmia (or definite EEG improvement if hypsarrhythmia was absent at baseline). For responders, the diagnostic and post-treatment EEG tracings were reviewed. Electroclinical remission was achieved in 21 of 39 patients (54%) receiving adrenocorticotrophic hormone, including 11/25 (44%) receiving a long course (typically 12 weeks) and 10/14 (71%) receiving a short course (typically four weeks). The mean time to clinical remission was 5.8 days (median: 5 days; range: 1-20 days). Only one patient responded beyond two weeks of treatment. This study provides Class IV evidence that among patients with infantile spasms, the response to adrenocorticotrophic hormone is most often determined early in the treatment course. Given the importance of rapid remission, clinicians should consider adding or changing treatment if infantile spasms do not resolve within two weeks of adrenocorticotrophic hormone initiation. Further study is needed to determine the optimal adrenocorticotrophic hormone regimen for infantile spasms.

Key words: infantile spasms, West syndrome, adrenocorticotrophic hormone, ACTH

Infantile spasms (IS) are seizures that are frequently associated with poor developmental outcome. With treatment, an average of 16% of children with IS may experience a favourable outcome (Frost and Hrachovy, 2003). Even those patients with less favourable outcomes can benefit from treatment with variable

degrees of developmental progress. Early and effective treatment may allow for improved developmental outcome (Riikonen, 2001; Eisermann *et al.*, 2003; Kivity *et al.*, 2004; Darke *et al.*, 2010).

Although successful treatment of IS with adrenocorticotrophic hormone (ACTH) was first described

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55 years ago (Sorel and Dusaucy-Bauloye, 1958), the optimal ACTH dose and duration has not been determined. The 2004 American Academy of Neurology and the Child Neurology Society practice parameter could not recommend an ACTH dose or duration for IS due to lack of evidence (Mackay *et al.*, 2004). The 2012 update of this practice parameter suggested that low-dose (e.g. 20 IU/day) ACTH may be as effective as high-dose (150 IU/m²/day) ACTH for the short-term treatment of IS (Go *et al.*, 2012). However, high-dose ACTH regimens remain in widespread use based on studies reporting high rates of electroclinical remission (Baram *et al.*, 1996). An optimal treatment duration has not been determined for either low-dose or high-dose regimens.

The 2010 United States consensus report on IS advocates for changes in treatment if early electroclinical remission is not achieved (Pellock *et al.*, 2010). Understanding when remission typically occurs with ACTH will help to inform decisions about early treatment changes among non-responders. When we established our IS management protocol in 2012, we changed our ACTH regimen to a four-week short course, to be consistent with the Food and Drug Administration-approved package insert for Acthar gel. This transition in regimen created a unique opportunity to compare outcomes between the adopted four-week short course and the previously used 12-week long course. We hypothesized that successful ACTH treatment is determined within two weeks of initiation, regardless of the duration of treatment. The aim of this study was to characterize the time from ACTH initiation to clinical remission among a cohort of ACTH responders.

Methods

We conducted a retrospective chart review of all IS patients managed at our institution from January 2009 to September 2013. Subjects were identified using an EEG database (search terms: “hypsarrhythmia” and “infantile spasms”) and hospital discharge codes (345.60, 345.61). Patients who did not receive ACTH were excluded. Two high-dose natural ACTH gel protocols were used during the study period; a 12-week regimen used prior to September 2012 published by Snead and colleagues (Snead *et al.*, 1983) and a four-week regimen used after September 2012 published by Baram and colleagues (Baram *et al.*, 1996). The 12-week ACTH regimen was dosed as follows: 75 IU/m² twice daily the first week, 75 IU/m² daily the second week, 75 IU/m² every other day the third and fourth week, and this was followed by a slow eight-week taper. The four-week ACTH regimen included two weeks at 75 IU/m² twice daily, followed by a rapid taper over two weeks.

We defined *ACTH response* as complete remission of clinical IS sustained for greater than or equal to 28 days beginning at any time within the ACTH course and remission of hypsarrhythmia (or definite EEG improvement if hypsarrhythmia was absent at baseline). A *relapse* was assigned if IS resumed after the initial remission. For ACTH responders, the diagnostic and post-ACTH EEG tracings were reviewed by a paediatric epileptologist (JRM) to assess for electrographic improvement.

The Mann-Whitney U, Pearson chi-square and Fisher exact tests were used to compare continuous and categorical variables. The log-rank test was used to compare time to remission between ACTH protocols. The one-way ANOVA was used to compare the time to remission between our cohort and two previously published cohorts. All statistical analyses were performed using SPSS Version 21 (SPSS Inc., Chicago, IL, USA). Significance was set at the 5% level. This study was approved by the Internal Review Board at Nationwide Children’s Hospital.

Results

Of 87 IS patients identified, 42 were treated with ACTH. One patient was excluded from analysis because the response to ACTH could not be determined and two patients were excluded because no post-ACTH EEG was performed. Of the remaining 39 patients, 21 responded to ACTH (54%). *Table 1* shows ACTH responders by treatment protocol, demographics and outcome. There was no significant difference in response between those receiving a long course (11/25, 48%) and a short course (10/14, 71%) of ACTH ($p=0.15$). Aside from the dates of treatment and the duration of treatment, there were no significant differences between patients in the long course and short course groups including: age at diagnosis ($p=0.39$), sex ($p=0.43$), age at ACTH initiation ($p=0.87$), and the number of patients with less than or equal to 30 days between IS onset and starting ACTH ($p=0.34$). Twenty-six percent of patients (10/39; seven in the long course group and three in the short course group) had unknown aetiology. There was no significant difference ($p=0.78$) in ACTH response when comparing patients with unknown aetiology to those with a documented aetiology. *Figure 1* shows similar ACTH response, regardless of aetiology. We identified one serious adverse event in the long course group. After failing to respond to ACTH, a patient with trisomy 21 died of sepsis eight days after the dose of ACTH was increased back to the initial dose of 150 U/m²/day, 20 days into the treatment course. There were no serious side effects in the short course group.

Table 1. ACTH responders by treatment protocol, demographics and outcome.

Pt/sex	Age at IS onset (months)	Aetiology	Development at IS onset	Hyps	Onset to ACTH (days)	Days to clinical remission [^]	ACTH start to EEG (days)	EEG Change	Relapse	f/u after starting ACTH (months)
1/M	8	Stroke	Abnormal	Yes	8	2	15	Remission	No	44
2/F	CD	Infection (meningitis)	Abnormal	Yes	CD	2	5	Remission	No	32.5
3/M	CD	HIE	Abnormal	Yes	CD	6	42	Remission	No	17.5
4/F	13.5	IVH	Abnormal	Yes	26	3	27	Remission	No	13.5
5/M	9.5	Unknown	Normal	No	10	5	41	Improved	No	3
6/M	7	HIE	Abnormal	Yes	2	20	130	Remission	No	27.5
7/F	4.5	Malformation	Normal	Yes	56*	1	4	Remission	No	30.5
8/M	3	Unknown	Abnormal	Yes	203*	1	35	Remission	Yes	25
9/M	CD	Genetic (ARX)	Abnormal	Yes	CD*	6	13	Remission	Yes	17
10/F	5	Malformation	Abnormal	Yes	28	6	25	Remission [#]	Yes	35
11/M	5	Stroke	Abnormal	Yes	115	7	25	Remission [#]	No	9.5
12/F	7	Trauma	Abnormal	Yes	23	10	17	Remission	No	22
13/M	14	Stroke	Abnormal	Yes	16	1	24	Remission	No	3.5
14/F	9.5	Chromo (Trisomy 21)	Abnormal	Yes	32	12	15	Remission	No	16
15/M	10	HIE	Abnormal	Yes	20	5	17	Remission	No	20
16/F	11.5	IVH	Abnormal	Yes	30	4	19	Remission [#]	No	10
17/F	3.5	Unknown	Normal	No	65	5	18	Improved	No	18.5
18/M	8.5	Trauma	Abnormal	Yes	131	2	18	Remission	No	18
19/M	6.5	Unknown	Normal	Yes	2	4	15	Remission	No	9
20/F	3	Stroke	Abnormal	No	47	10	15	Improved	Yes	16.5
21/F	4	Unknown	Normal	Yes	6	10	15	Remission	No	9

Light grey long course protocol; dark grey: short course protocol.

*ACTH as the second treatment for infantile spasms (ACTH was the first treatment for infantile spasms in all other patients).

[^]First day free of any infantile spasms.

[#]Follow-up EEG did not include sleep.

Pt: patient number; M: male; F: female; IS: infantile spasms; HIE: hypoxic-ischaemic encephalopathy; IVH: intraventricular haemorrhage; malformation: malformation of cortical development; Chromo: chromosomal; CD: cannot determine; Hyps: Hypsarrhythmia; f/u: follow-up.

The date of IS onset could be determined in 32 patients. For these patients, the median interval from IS onset to the start of ACTH (treatment lag) was 29 days (mean: 43.6 days; range: 2-203; interquartile range [IR]: 9.25-63). The treatment lag did not significantly differ based on ACTH response (responders: median of 24.5 days, range of 3-95, IR of 9.5-58; non-responders: median of 27 days, range of 3-95, IR of 8-79; $p=0.72$) or protocol (long course: median of 28 days, range of 2-203, IR of 9-83; short course: median of 31 days, range of 2-131, IR of 13.5-59; $p=0.92$).

The mean time to clinical remission (first seizure-free day) for the 21 responders was 5.8 days (median: 5 days; range: 1-20). *Figure 2* illustrates the percent of

seizure remission as a function of ACTH treatment days; time to remission did not significantly differ between the long course and short course groups ($p=0.51$). The patient with clinical remission at 20 days did so only after a second course of high-dose ACTH (75 IU/m² twice daily) was started 19 days into treatment. Among responders, this was the only example of a protocol deviation identified. A relapse of IS after an initial remission was uncommon in both protocols (three in the long course group and one in the short course group).

Among ACTH responders, the median interval from ACTH initiation to the post-ACTH EEG was 18 days (mean: 25.5 days; range: 4-130; IR: 15-26); this interval

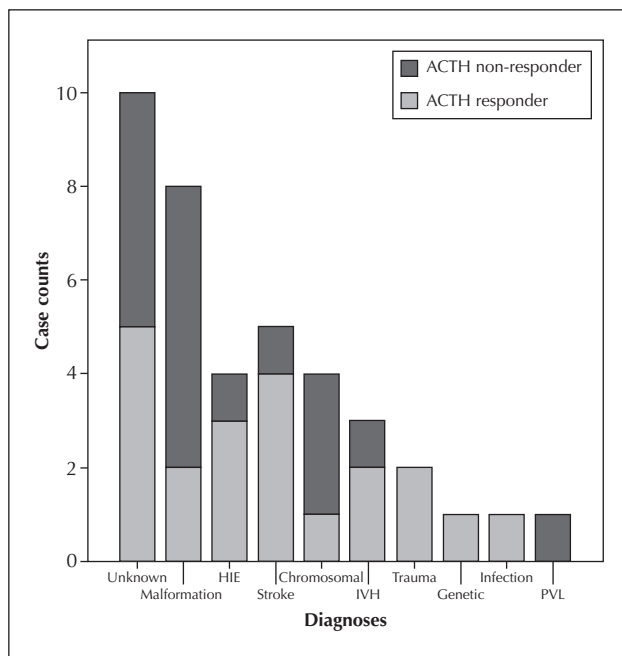


Figure 1. The response to ACTH by diagnostic aetiology. Malformation: malformation of cortical development; HIE: hypoxic ischaemic encephalopathy; IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia.

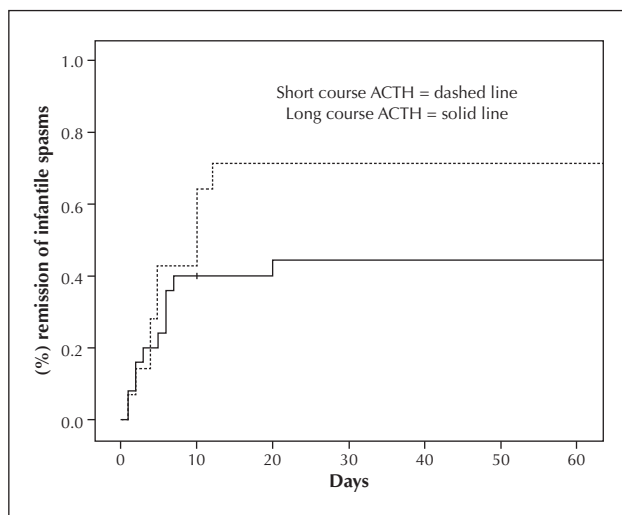


Figure 2. One-minus-survival plot illustrating the percent of seizure remission as a function of ACTH treatment days. The dashed line represents the short course ACTH protocol ($n=14$); the solid line represents the long course ACTH protocol ($n=25$). Time to remission did not differ by protocol; $p=0.26$ (log-rank test).

was not significantly different between the long course (median: 25 days; range: 4-130; IR: 13-41) and short course (median: 17 days; range: 15-24; IR: 15-18) groups ($p=0.25$). For ACTH responders, the median duration from ACTH initiation to last follow-up was 25 months (mean: 23 months; range: 3-44) in the long course group and 16.3 months (mean: 14.3 months; range: 3.5-22) in the short course group (table 1).

Discussion

Our study of IS patients is the first to compare the number of days to clinical remission in a group of consecutive ACTH responders treated with either a short course or long course of ACTH. In our cohort, response was determined within two weeks of starting ACTH in 96% and within three weeks in 100%. Additional treatment with ACTH beyond three weeks (for up to 12 weeks) did not yield additional responders. Although not powered for this analysis, there was no significant difference in the response rates for those treated with a long course (44%) or a short course (71%) of ACTH.

We identified two other studies that reported the time to remission in cohorts that received the same ACTH regimens used in our study. In the study by Snead and colleagues (utilizing the same high-dose, long course ACTH regimen used in our study), the mean time to clinical remission was 5.9 days in 14 responders (Snead *et al.*, 1989). In the study by Baram and colleagues (utilizing the same high-dose, short course regimen used in our study), the mean time to clinical remission was approximately 3.2 days in 13 responders (Baram *et al.*, 1996). Our mean time to clinical remission of 5.8 days matches the 5.9 days reported by Snead and colleagues, and is not statistically different from the 3.2 days reported by Baram and colleagues ($p=0.15$). If we combine our mean response time with the response times from these two prior studies, the mean time to clinical remission is about five days, with the response to ACTH determined within two weeks in 94% (44/47) of responders and within three weeks in 100%.

In their study, Snead and colleagues had two patients with clinical remission beyond two weeks of starting ACTH (one at 15 days and one at 21 days) (Snead *et al.*, 1989). One of our patients experienced clinical remission 20 days after ACTH initiation. While cause-and-effect is not proven, this patient's ACTH was increased back to 75 IU/m² twice daily, 19 days into the original treatment protocol. Despite this protocol deviation, we included this patient in our analysis as a long course ACTH responder. However, our current treatment protocol does not include the reintroduction of high-dose ACTH following an initial treatment failure due to limited available safety data.

One argument for the use of longer ACTH protocols has been the possible reduction in the rate of relapse. The number of relapses in our study was small (three in the long course group and one in the short course group). Although the low relapse rate following the short course of ACTH is somewhat reassuring, our small study size and the brief duration of follow-up in two patients (one due to death and another lost to follow-up) prevents us from drawing conclusions about relapse and the duration of ACTH treatment.

While the rate of electroclinical remission was not the primary outcome measure, the rate of electroclinical remission in this study was well within the range reported for IS clinical trials (42-87%; Pellock *et al.*, 2010) and nearly identical to the rate reported in the Class I study by Hrachovy and colleagues (1994). Our inclusion of all IS cases could have biased our results, with a lower overall remission rate compared to some prospectively designed clinical trials where the most severely affected patients might be excluded. However, our electroclinical remission rate may appropriately represent clinical practice.

In addition to the retrospective study design and small study population, our study included other limitations. Given that our ACTH cohorts were treated in two different time periods, we cannot exclude the possibility that other confounders affected our results. Our study also does not address the pharmacodynamic differences between natural and synthetic ACTH or the differences between high-dose and low-dose ACTH. For example, differences in potency may affect the timing of response. In addition, our EEG review was not blinded to the duration of ACTH treatment and three post-ACTH EEGs did not include sleep. We acknowledge the importance of sleep during the EEG, given that findings to suggest an IS-associated epileptic encephalopathy may be present only during sleep (Watanabe *et al.*, 1993). The clinical response and the absence of any subsequent signs of IS in these patients over a mean of 18 months (range: 10-35) of follow-up provides some reassurance that they experienced a remission without relapse. Although our current protocol includes a post-treatment overnight EEG to confirm electroclinical remission, this was not done consistently in this cohort. The absence of prolonged EEG monitoring to confirm electroclinical remission in ACTH responders is a shortcoming of this study. Of the responders who had a post-ACTH EEG, all but one had the EEG within 42 days (table 1); this outlier EEG was performed four months after starting ACTH, raising the possibility of spontaneous remission (the rate of which is estimated to be 7% at four months) (Hrachovy *et al.*, 1991).

This study provides Class IV evidence that among IS patients, the response to ACTH is determined early in the treatment course for most patients. Given the

importance of rapid remission (Darke *et al.*, 2010), clinicians should consider adding or changing treatment if IS do not resolve within two weeks of ACTH initiation. While we acknowledge that an IS remission might occur after three weeks in some patients, the low likelihood of a late response may not justify the potential for adverse events with long duration ACTH treatment. Further study is needed to determine the optimal ACTH regimen for IS.

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The authors have no conflicts of interest to declare.

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