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Authors

Hussain, Shaun A
Shinnar, Shlomo
Kwong, Grace
et al.

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Treatment of infantile spasms with very high dose prednisolone before high dose ACTH

Shaun A. Hussain, MD, MS[1], **Shlomo Shinnar, MD, PhD**[2], **Grace Kwong**[1], **Jason T. Lerner, MD**[1], **Joyce H. Matsumoto, MD**[1], **Joyce Y. Wu, MD**[1], **W. Donald Shields, MD**[1], and **Raman Sankar, MD, PhD**[1]

[1]Department of Pediatrics, Division of Neurology, Mattel Children's Hospital and David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[2]Departments of Neurology, Pediatrics, and Epidemiology and Population Health, Montefiore Medical Center, Albert Einstein College of Medicine Bronx, New York, USA

Summary

Objective—This study investigated the short-term response to a standardized hormonal therapy protocol for treatment of infantile spasms.

Methods—Twenty-seven children with video-EEG confirmed infantile spasms received very high dose (8 mg/kg/day, max 60 mg/day) oral prednisolone for 2 weeks. Response (absence of both hypsarrhythmia and spasms) to prednisolone was ascertained by repeat overnight video-EEG. Responders were tapered off over 2 weeks and non-responders were immediately transitioned to high dose (150 IU/m2/day) intramuscular ACTH for 2 additional weeks. Response was again determined by overnight video-EEG after ACTH therapy.

Results—Sixty-three percent (17/27) of patients responded completely to prednisolone. Subsequently, 40% (4/10) of prednisolone non-responders exhibited a complete response after an additional 2-week course with ACTH. Among 27 subjects with median follow-up of 13.5 months (interquartile range 4.8-25.9), 12% (2/17) of prednisolone responders and 50% (2/4) of ACTH responders experienced a relapse between 2 and 9 months after initial response.

Corresponding Author: Shaun A. Hussain, MD, MS, Assistant Clinical Professor of Pediatrics, Division of Pediatric Neurology, Mattel Children's Hospital, David Geffen School of Medicine at UCLA, 22-474 Marion Davies Children's Center, Box 951752, Los Angeles, CA 90095-1752, USA, Phone: (310) 825-6196, Fax: (310) 825-5834, shussain@mednet.ucla.edu.

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Significance—Very high dose prednisolone demonstrated significantly higher efficacy than previously reported for lower doses in prior studies. High dose ACTH may be superior to very high dose prednisolone, and in lieu of a definitive clinical trial, the choice between prednisolone and ACTH for initial treatment of infantile spasms remains controversial.

Keywords

hypsarrhythmia; corticotropin; ACTHar; corticosteroids; West syndrome

Introduction

Infantile Spasms (IS) is an uncommon but often devastating form of epilepsy that typically strikes children in the first year of life (Shields, 2006). Usually provoked by one of many structural, genetic, or metabolic etiologies, IS manifests with clusters of a distinct seizure-type (spasms), and is often accompanied by an electroencephalography (EEG) pattern known as hypsarrhythmia (Hrachovy et al., 1984). Unsuccessful treatment, as well as delay in definitive treatment, are associated with reductions in neurodevelopmental outcome (O'Callaghan et al., 2011). Among pharmacologic therapies for IS, hormonal therapies such as intramuscular adrenocorticotropic hormone (ACTH) (Snead et al., 1989; Hrachovy et al., 1994; Baram et al., 1996), and oral corticosteroids (prednisone or prednisolone) (Lux et al., 2004; Kossoff et al., 2009) appear to be most efficacious. There is no consensus on the role of oral corticosteroids in the first-line treatment of IS (Pellock et al., 2010).

In the present study we examined the short-term efficacy of a standardized hormonal therapy protocol for IS. Based on contemporary reports of success with high dose prednisolone albeit without video-EEG confirmation of response (Lux et al., 2004; Kossoff et al., 2009), cost, ease of administration, and an effort to avoid even small delays in the initiation of definitive therapy, UCLA adopted a protocol in which patients with IS received prednisolone for two weeks with immediate transition to ACTH in those patients who did not respond to prednisolone. In contrast to prior studies in which “high dose” prednisolone dosage was 40 or 60 mg/day (approximately 4 to 8 mg/kg/day), we implemented a weight-based dosing scheme (8 mg/kg/day), with a maximum dose of 60 mg/day. We have therefore used the term “very high dose” to distinguish our protocol from both these non-weight-based “high dose” regimens as well as the traditional 2 mg/kg/day protocol, which itself is a high dose from the perspective of other corticosteroid responsive diseases. Importantly, overnight video-EEG was used to confirm spasms at protocol initiation and to verify responses to prednisolone and ACTH.

Methods

Participants

In a retrospective records review, children with video-EEG confirmed infantile spasms, with or without hypsarrhythmia, treated at the Mattel Children's Hospital at UCLA between April, 2009 and November, 2012 were identified. We included all patients without history of prior hormonal therapy who followed the standardized hormonal treatment protocol (outlined below). A history of prior hormonal therapy was the sole exclusion criterion for this analysis.

Treatment Protocol

As per the standard of care at UCLA, all children with video-EEG confirmed IS who were deemed appropriate candidates for hormonal therapy followed the UCLA protocol: On the day of diagnostic confirmation, treatment with oral prednisolone solution (15 mg/mL) was initiated at 8 mg/kg/day, divided in 3 daily doses, with a maximum daily dose of 60 mg.

After 2 weeks, all patients with clinical response to prednisolone based on parental report underwent repeat overnight video-EEG to confirm resolution of spasms and determine whether hypsarrhythmia was present. Those patients with complete response (resolution of spasms and lack of hypsarrhythmia) at the 2-week time point were tapered off prednisolone over 2 additional weeks. The remaining patients with continued spasms and/or hypsarrhythmia were all immediately transitioned to intramuscular biologic ACTH (H.P. ACTHar Gel, Questcor Pharmaceuticals) with a dosage of 150 IU/m^2/day, divided in two daily doses (Baram et al., 1996). Prednisolone was discontinued without taper at the time of ACTH initiation. Again, after 2 additional weeks, all patients with parental report of improvement underwent repeat overnight video-EEG assessment. Those patients with complete response were then tapered off ACTH over 2 weeks. The remaining patients without a complete response continued ACTH, tapered off ACTH, or received alternative therapies at the discretion of the treating neurologist. The protocol is illustrated in Figure 1.

EEG Criteria

The identification of IS and the determination of whether hypsarrhythmia was present or absent was made on a routine clinical basis. Electroencephalographers were not blinded with regard to treatment status of patients. In this study, we use the term hypsarrhythmia to denote classic hypsarrhythmia (high voltage, disorganization, and multifocal epileptiform discharges) as well as so-called modified and atypical variants (Hrachovy et al., 1984).

Statistical Methods

Comparisons of proportions and medians were accomplished using the Fisher exact test and Wilcoxon rank-sum test, respectively, with STATA software (version 11, College Station, Texas, USA). Continuous summary data were presented as median and interquartile range based on non-parametric distributions where appropriate.

Standard Protocol Approvals

This use of human subjects and the analyses presented here were approved by the Institutional Review Board at UCLA. As a retrospective records review, the requirement for written informed consent was waived.

Results

The study cohort was highly selected: 91 patients with IS were evaluated at UCLA during the study period (most often seen as a second opinion), and only 30 followed the protocol here. The majority did not enter the protocol because (1) they had previously failed an adequate trial of ACTH, (2) the risk/benefit ratio of any hormonal therapy was unfavorable, or (3) alternative non-hormonal therapies were pursued (e.g. vigabatrin, surgery, ketogenic diet). Three of 30 patients who followed this protocol were excluded on the basis of prior hormonal therapy, including one patient with tuberous sclerosis complex (TSC) who responded to prednisolone. Many patients had undergone at least limited evaluations at other institutions and had received a trial of one or more non-hormonal therapies including vigabatrin. Demographic characteristics are summarized in Table 1. Twenty-seven patients received hormonal therapy for IS according to the UCLA protocol outlined above. Please see Table 2 for detailed etiologic, electroencephalographic, and treatment response data. Hypsarrhythmia was observed on baseline EEG in 18 (67%) patients. The remaining patients exhibited significant electrographic abnormalities which did not satisfy formal criteria for hypsarrhythmia but were nevertheless compatible with a diagnosis of IS. Of note, two patients (Pts 14, 15) exhibited hypsarrhythmia without spasms at protocol entry; both patients had EEG-proven spasms on recent studies in the context of prior therapies. Seventeen of 27 patients (63%) completely responded to prednisolone at the 2-week time

point. Of the 10 patients who did not respond to prednisolone, four subsequently responded to ACTH (40%). The cumulative short-term response rate was 78% (21/27). Of note, three of four patients (Pts 19 – 21, Table 2) who ultimately responded to ACTH had resolution of hypsarrhythmia but continued spasms after two weeks of prednisolone therapy.

After initially successful treatment with prednisolone, two patients (Pts 5, 11) had a relapse of spasms after two and five months, respectively. One patient was rechallenged with prednisolone and responded once again, and has remained seizure-free for three months at most recent follow-up. The second patient is now receiving other nonhormonal therapies. Among the four patients who responded to ACTH, two (Pts 20, 21) relapsed after nine and four months, respectively. Neither patient was rechallenged with hormonal therapy, and both are receiving nonhormonal therapies, including the ketogenic diet. None of the patients with relapse of IS have exhibited a relapse of hypsarrhythmia. Of note, two patients (Pts 22, 26) did not undergo video-EEG after ACTH therapy as clinical spasms were either unchanged or more severe with respect to frequency; the UCLA protocol requires video-EEG confirmation of treatment response rather than treatment failure. With respect to demographic variables, etiology, age of onset, treatment delay, and presence of hypsarrhythmia prior to prednisolone, there were no significant differences between prednisolone responders and non-responders. Similarly, there were no differences between those patients who responded to any hormonal therapy and those who failed sequential trials of both prednisolone and ACTH. Of note, these comparisons were quite underpowered.

Discussion

Few studies have evaluated the efficacy of corticosteroids or ACTH with video-EEG verification of clinical and electrographic response, and this is the first study to report video-EEG confirmed response rate to treatment with high dose prednisolone (>2 mg/kg/day). Among those utilizing video-EEG confirmation, as illustrated in a recent meta-analysis (Arya et al., 2012), compelling data indicate that traditional 2 mg/kg/day prednisone is inferior to high dose ACTH (150 IU/m^2/day, twice-daily administration). This was based on a pair of studies in which the response rate to high dose ACTH was 90% (Snead et al., 1989; Baram et al., 1996). An additional study yielded a response rate of just 50% among 26 patients who received a long-duration, high-dose course of ACTH (Hrachovy et al., 1994), though this study utilized a once-daily administration protocol which may have impacted pharmacokinetics and response rate (Snead et al., 1989; Pellock et al., 2010; Arya et al., 2012) and was therefore omitted from in the meta-analysis below. Most recently, as part the Canadian Pediatric Epilepsy Network trial evaluating flunarizine as a neuroprotective agent in IS, an impressive 24 of 30 (80%) patients who did not respond to a short course of vigabatrin subsequently responded to a two-week course high-dose synthetic ACTH (∼150 IU/m2/day, every-other-day administration), with outcome assessment determined by a 1-hour wake-sleep EEG (Bitton et al., 2012).

In contrast to low response rates to traditional dose prednisone (2 mg/kg/day), several contemporary reports that did not utilize video-EEG confirmation of response suggested that the response rate to high dose prednisolone (∼4 to 8 mg/kg/day) is superior to traditional dose prednisone and may not differ from ACTH (Lux et al., 2004; Kossoff et al., 2009; Ware et al., 2012). Although a lack of video-EEG confirmation may inflate response rates (Pellock et al., 2010; Arya et al., 2012), these reports nevertheless inspired the protocol adopted at UCLA and the analysis presented here.

Our 63% response to very high dose prednisolone is significantly higher than the aforementioned 31% pooled response to traditional dose prednisone (Hrachovy et al., 1983; Baram et al., 1996) ($p < 0.05$, Fisher exact), and lower than the response rate to high dose

ACTH of 90% among 30 total patients (Snead et al., 1989; Baram et al., 1996). Although these meta-analytic comparisons suggest that very high dose prednisolone is more efficacious than traditional dose prednisone and inferior to high dose ACTH, these comparisons must be interpreted with caution. The use of historical comparators clearly precludes randomization, and ignores potentially critical confounders, especially with regard to the demographic and etiologic characteristics of each study population. Moreover, there is ongoing debate regarding the ideal dosage of ACTH (Go et al., 2012), and uncertainty regarding the equivalence of biologic and synthetic preparations of ACTH.

Children with IS are highly heterogeneous and we suspect our observed response rate to very high dose prednisolone is an underestimate of "true" efficacy as our patients were relatively older, had generally failed multiple treatments prior to protocol entry (including vigabatrin), and had often experienced long delays between diagnosis and protocol entry—all factors which are thought to reduce the likelihood of response to an effective agent (Pellock et al., 2010). Had this protocol been promptly administered to a relatively younger and treatment-naïve population, our short-term response rate might have been substantially better. Conversely, our observation that 4 patients responded to ACTH after incomplete response to prednisolone suggests that ACTH may be superior to high dose prednisolone but the numbers are small. Furthermore, some of the prednisolone responders in this study may have been partial responders to therapies that predated prednisolone, and as such, our prednisolone response rate may be inflated to some extent. Moreover, this study is not a formal clinical trial, but simply a report of our experience with a standardized protocol. Key limitations include lack of a control group, lack of standardized and blinded developmental assessments, limited follow-up time, and small study population. A large-scale, multicenter, randomized, and blinded trial is required to conclusively determine whether there is a difference in efficacy between high dose ACTH and very high dose prednisolone.

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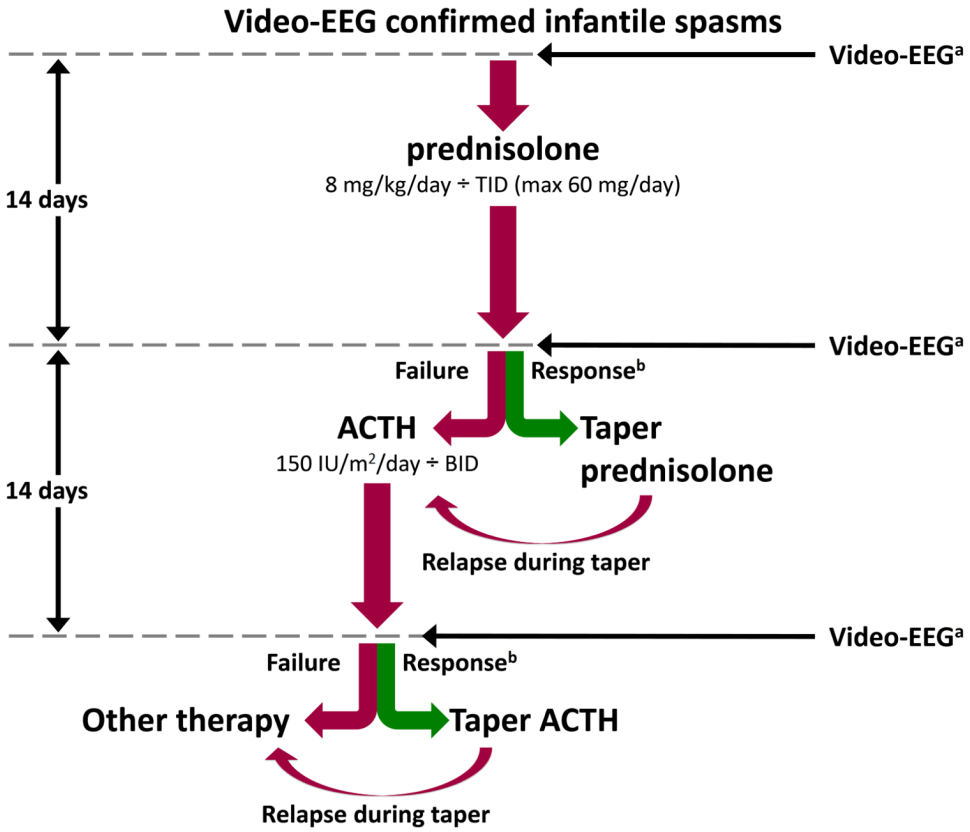

Figure 1.

The UCLA Hormonal Therapy Protocol. [a]All video-EEG evaluations were inpatient overnight studies. [b]Response requires video-EEG confirmation of freedom from both spasms and hypsarrhythmia.

Table 1

Characteristics of the study population.

Demographics and Clinical Characteristics	
Total patients, n	27
Sex, male, n (%)	18 (67%)
Age of onset of IS, months, median (IQR[a])	6.7 (4.8 - 12.5)
Age at protocol entry, months, median (IQR)	10.8 (6.7 - 17.9)
Hypsarrhythmia present at protocol entry, n (%)	18 (67%)
Previous or concurrent vigabatrin treatment, n (%)	9 (33%)
Delay from diagnosis to protocol entry, months, median (IQR)	2.0 (0.5 - 4.6)
Duration of follow-up, months, median (IQR)	13.5 (4.8 - 25.9)

[a] Interquartile range

Table 2

Patient Data

Pt	Age of Onset (mo)	Prior Tx	Etiology	Tx Delay (mo)	EEG 1[a]	PRED Resp	EEG 2	ACTH Resp	EEG 3	Relapse (mo)	Follow-up (mo)
1	7.6	TPM, CLN	Ch 7 deletion	3.2	S/-	+	-/-	NA	NA	-	13.5
2	4.3	None	Cryptogenic	2.4	S/-	+	-/-	NA	NA	-	20.9
3	13.4	OXC	TBI	1.3	S/-	+	-/-	NA	NA	-	21.5
4	4.9	None	Diffuse PMG	0.2	S/-	+	-/-	NA	NA	-	2.9
5			Tetrasomy 15q	5.3	S/-	+	-/-	NA	NA	2 mo	3.5
6	4.9	None	Stroke	0.3	S/-	+	-/-	NA	NA	-	1.2
7	3.0	ZNS	Unknown +DD	15.9	S/H	+	-/-	NA	NA	-	42.2
8	4.4	PHB, LEV	IVH	0.6	S/H	+	-/-	NA	NA	-	38.1
9	23.5	LEV, ZNS, B6, VGB	PVL	2.0	S/H	+	-/-	NA	NA	-	4.6
10	20.0	None	Unknown +DD	19.5	S/H	+	-/-	NA	NA	-	27.2
11	5.4	LEV	HIE	0.9	S/H	+	-/-	NA	NA	5 mo	21.7
12	24.0	OXC	Unknown +DD	0.3	S/H	+	-/-	NA	NA	-	12.6
13	6.2	B6	Cryptogenic	0.5	S/H	+	-/-	NA	NA	-	11.3
14	14.4	VGB, ZNS	T21, Stroke	3.1	-/H	+	-/-	NA	NA	-	5.8
15	6.0	VGB, B6, ZNS	VOGM, ICH	9.5	-/H	+	-/-	NA	NA	-	0.5
16	7.9	LEV, PHB, OXC, VGB	AVM, ICH	2.9	S/H	+	-/-	NA	NA	-	3.8
17	17.9	LEV	FCD	0.5	S/H	+	-/-	NA	NA	-	5.0
18	7.6	None	Unknown +DD	0.5	S/-	-	S/-	+	-/-	-	10.2
19	12.2	TPM	SCN1A	1.1	S/H	-	S/-	+	-/-	-	29.6
20	6.7	VGB	Stroke	4.0	S/H	-	S/-	+	-/-	9 mo	18.8
21	3.1	LAC, CLN, LEV	PMG, ACC	11.3	S/H	-	S/-	+	-/-	4 mo	11.7
22	12.0	LEV, ZNS, VGB, CLN	FCD	14.9	S/-	-	S/-	-	None	-	31.7
23	12.7	TPM, ZNS, VGB	Unknown +DD	26.4	S/-	-	S/-	-	S/-	-	24.7
24	3.1	LEV, PHB, VPA	NKH	3.8	S/H	-	S/H	-	S/H	-	40.1
25	4.7	ZNS, VGB	DEND	1.9	S/H	-	S/H	-	S/H	-	29.0
26	4.1	TPM	T21	0.6	S/H	-	S/-	-	None	-	1.2
27	6.8	TPM	Lissencephaly	0.4	S/H	-	S/-	-	S/-	-	13.9

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[a] EEG 1 was performed prior to prednisolone, EEG 2 after prednisolone, and EEG 3 after ACTH.

Pt, patient; Tx, treatment; PRED, prednisolone; ACTH, adrenocorticotropic hormone; TPM, bottomiramate; CLN clonazepam, OXC, oxcarbazepine; VGB, vigabatrin; B6, pyridoxine; ZNS, zonisamide; PHB, phenobarbital; LEV, levetiracetam; DZP, diazepam; LAC, lacosamide; Ch, chromosome; TBI, traumatic brain injury; PMG, polymicrogyria; +DD, developmental delay prior to onset of infantile spasms; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; T21, trisomy 21; VOGM, vein of galen malformation; ICH, intracerebral hemorrhage; AVM, arteriovenous malformation; FCD, focal cortical dysplasia; NKH, nonketotic hyperglycinemia; DEND, syndrome of developmental delay, epilepsy, and neonatal diabetes; S, spasms present; H, hypsarrhythmia present; "−", feature absent or incomplete response, as appropriate; "+"; complete response; NA, not applicable.