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Cerebrospinal Fluid Corticotropin and Cortisol Are Reduced in Infantile Spasms

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Abstract

Infantile spasms respond to ACTH, and levels of the hormone in cerebrospinal fluid of untreated infants with this disorder were found to be lower than in age-matched controls. In this study we analyzed cerebrospinal fluid Cortisol and ACTH using improved immunoassays in a larger cohort of infants with infantile spasms. Analysis of 20 patients and 15 age-matched controls revealed significantly lower levels of both ACTH and Cortisol in the cerebrospinal fluid. These data, combined with the efficacy of ACTH and glucocorticoids for infantile spasms, support an involvement of the brain-adrenal-axis in this disorder.

Introduction

The etiology of infantile spasms (IS) has not been resolved [1–3]. The seizures are treated with ACTH or prednisone, with a response rate of 50–88% [1,3–5]. The mechanisms by which these hormones suppress the seizures and normalize the EEG are not fully understood, yet may help clarify the pathophysiology of this disorder [2,3]. The “all-or-none” disappearance of spasms often within days, and the persistence of the effect upon hormone withdrawal, is consistent with a neuroendocrine mechanism [3,6]. We have previously found a low cerebrospinal fluid (CSF) level of ACTH in untreated infants with IS compared with age-matched controls [6]. A trend toward decreased Cortisol did not reach statistical significance ($P = .08$), but Cortisol values were available only from 12 patients and 9 controls. This report summarizes the study of CSF Cortisol and ACTH in a larger cohort of patients with IS and age-matched controls.

Methods

Patients and Controls

Patients consisted of 20 infants (3–14 months old) fulfilling criteria for IS [7], all with hypsarrhythmia or modified hypsarrhythmia at the time of spinal tap (Table 1). Four infants with no etiology for their IS and a normal neurodevelopmental assessment were defined as cryptogenic or idiopathic [8]. Infants with abnormal neurodevelopmental examination and no proven etiology were classified as “symptomatic with unknown etiology.” Patients underwent a lumbar puncture as part of an evaluation for the etiology of the syndrome. No patient had received ACTH or prednisone prior to the procedure.

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Age-matched controls were infants undergoing lumbar puncture for various reasons (Table 2). The clinical characteristics of both groups of patients are delineated in Tables 1 and 2; five patients and controls were included in a previous report [6]. The study of CSF was approved by the Internal Review Board for human studies of Childrens Hospital Los Angeles, and Kaiser-Permanente. Los Angeles.

CSF Handling, Hormone Assays, and Statistical Considerations

CSF was collected in ice-chilled tubes and immediately stored at −80°C. Aliquots were lyophilized for Cortisol assay; for ACTH, improved methods did not require lyophylization. New CSF samples and those from previously reported infants (five each, patients and controls) were assayed together.

ACTH samples were subjected to a two-point antibody ACTH assay (Allegro ACTH IRMA. Nichols Institute, San Juan Capistrano. CA). Assay sensitivity was 5 pg/ml; interassay variability was 8%. Cortisol was measured using a commercial radioimmunoassay (6, ICN Irvine, CA).

Results

Individual values of CSF ACTH and Cortisol are shown in Tables 1 and 2. Mean age of IS infants was 6.73 ± 0.6 months and of controls 7.8 ± 1.9 months (difference not significant). Median ages were 5 months for controls and 6 months for the IS group. This discrepancy reflects a wider age spread in the controls.

Summary and statistical analyses of hormonal values are presented in Table 3. Both ACTH and Cortisol levels were markedly and significantly reduced in IS patients as compared with age-matched controls. The larger sample size confirmed the trend to lower Cortisol levels in patients. The more reliable IRMA technique for ACTH (compared with radioimmunoassay) validated the lower levels in infants with IS and resulted in a smaller variance. This increased statistical significance ($P = .0029$, Mann-Whitney U test).

Among patients with IS, 4 of 21 (19%) were cryptogenic, with a normal neurodevelopmental examination. There was a trend toward lower Cortisol levels in this group (1.25 ± 0.46 ng/ml) compared with infants with abnormal examination regardless of the presence of a defined etiology (1.57 ± 0.46 ng/ml). ACTH levels in 3 normal infants (30.33 pg/ml) did not distinguish them from those with abnormal neurologic examinations.

Discussion

In a cohort of untreated infants with IS, CSF ACTH and Cortisol were lower than in age-matched controls, suggesting an abnormal brain-adrenal axis. CSF ACTH does not reflect peripheral levels, and may be a marker for central nervous system abnormalities of the CRH-ACTH-cortisol cascade. The findings do not distinguish between under-production of ACTH and Cortisol, as suggested by Riikonen [2], or downregulation of ACTH production due to chronic exposure to the ACTH stimulator, corticotropin releasing hormone (CRH) [3,8].

Chronic infusion of synthetic CRH into the cerebral ventricles of the rat leads to desensitization of CRH receptors and to lower CSF ACTH [9]. Our findings are thus consistent with an increase of CRH in the central nervous system of patients with IS. CRH is a convulsant, with strong age-specificity to infancy [10]. One may speculate that CRH plays an epileptogenic role in IS and is associated with decreased CSF ACTH and Cortisol [3,6]. As CRH receptors peak in infancy [11], seizures may only occur at that age. The typical

response of IS to ACTH, in view of general resistance to conventional antiepileptic drugs, is concordant with this hypothesis. Further, the unique response pattern of the seizures to hormonal therapy (abrupt, “all-or-none” disappearance within days, without recurrence on discontinuation of therapy) suggests neuroendocrine mechanisms for ACTH/prednisone efficacy. This may involve a negative feedback suppression of the synthesis or secretion of CRH [3,6], which lasts throughout the period of high CRH receptor abundance [11].

Unlike others [12; R. Riikonen, personal communication], we did not find significant differences between infants with “cryptogenic” and “symptomatic” IS. Our study, like other reports, suffers from the small numbers of truly normal (“idiopathic-cryptogenic”) infants. In summary, untreated patients with IS have significantly low CSF ACTH and Cortisol. The relevance of this finding to the etiology of the disorder deserves further study. We are assessing the effect of hormonal therapy on these CSF parameters.

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Table 1

Characteristics of patients with infantile spasms

No.	Age (mos)/Sex	Etiology	ACTH (pg/ml)	Cortisol (ng/ml)
1	6/M	Brain malformation	19	1.0
2	3/F	Unknown, abnormal	34	3.37
3	10/M	Unknown, abnormal	45	—
4	6/F	Cryptogenic, normal	33	2.5
5	7/F	Tuberous sclerosis	27	1.2
6	10/F	Cryptogenic, normal	24	1.75
7	6/F	Cryptogenic, normal	34	0.37
8*	5/F	Unknown, abnormal	48	—
9	3.5/M	Congenital cytomegalovirus	24	1.25
10	9/M	Unknown, abnormal	20	—
11	8/M	Unknown, abnormal	21	—
12	6/F	Multiple anomalies	21	0.87
13	6/M	Down syndrome	40	1.25
14*	6/F	Congenital malformation	24	1.25
15*	3/M	Unknown, abnormal	12	1.25
16*	12/M	Congenital hydrocephalus	50	2.75
17	5/F	Bacterial meningitis	26	0.9
18*	11/M	Congenital malformation	38	0.55
19	6/M	Unknown, abnormal	29	3.25
20	6/F	Cryptogenic, normal	—	0.37

* Reported previously [6].

Table 2

Characteristics of control infants

No.	Age (mos)/Sex	Diagnosis	ACTH (pg/ml)	Cortisol (ng/ml)
1	14/F	Seizures	27	—
2	17/M	Acute ataxia	58	2
3	3/M	Seizures	45	—
4	5/F	Status epilepticus	34	1.6
5	2/F	“Rule-out herpes”	33	2.5
6	2.5/M	Seizures	38	1.35
7	28/M	Seizures, delayed	46	5.25
8	12/M	Seizures	28	1.1
9	2/M	Seizures	36	1.6
10	3.5/M	Seizures	49	4.0
11*	18/M	Ataxia	77	—
12*	1/M	Seizures	60	2.9
13*	5/M	Viral syndrome	42	3.75
14*	10/M	Febrile seizure	33	6.0
15*	3/M	Seizures	75	1.63

* Reported previously [6].

Table 3

CSF hormones in infantile spasms: Summary

Hormone	Controls (n)	IS(n)	*P*
Cortisol (ng/ml)	2.81 ± 0.46 (12)	1.49 ± 0.24 (16)	.0094 *
ACTH (pg/ml)	45.6 ± 4.0 (15)	29.9 ± 2.4 (19)	.0029 *

Values are means ± standard error.

* Two-tailed; Mann-Whitney U test.

Abbreviation:
IS = Infantile spasms