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Topiramate and Adrenal Cortico-tropic Hormone as Initial Treatment of Infantile Spasms

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Abstract

Historically, adrenal cortico-tropic hormone (ACTH) was used as first line treatment for infantile spasms, however there has been increasing use of topiramate as initial therapy. Here we report a retrospective study of ACTH and topiramate as initial treatment of infantile spasms. The neurology patient database at the Children's Hospital of Philadelphia was searched using the ICD-9 code for infantile spasms, and 50 patients were randomly chosen for chart review. We identified thirty-one patients receiving either ACTH or topiramate monotherapy (ACTH, n = 12, topiramate n = 19) as a first line treatment for infantile spasms. Twenty-six patients were symptomatic and five cryptogenic. Six patients treated with ACTH had resolution of clinical spasms and hypsarrhythmia within a month, but three relapsed. Four of the nineteen patients treated with topiramate eventually, though over a period of 0,1,8 or 69 months, had resolution of spasms and hypsarrhythmia.

Keywords

Infantile spasms; ACTH; topiramate

Introduction

The American Academy of Neurology and the Child Neurology Society supported the use of ACTH for the treatment of infantile spasms, though the dose and duration of treatment was not specified¹. They also suggested that vigabatrin might be effective. The efficacy of ACTH for resolution of clinical spasms has varied from as low as 33% to as high as 100%, with relapse rates of 8 to 50%²⁻⁵. Resolution of hypsarrhythmia on the EEG with ACTH also varied with rates as low as 21% and as high as 100%. In most studies, cryptogenic patients fared better than symptomatic patients. There are however numerous other treatments that have been utilized to various extents for the treatment of infantile spasms including, B6, nitrazepam, valproic acid, prednisone, leviteracetam, zonisamide and topiramate⁶⁻¹⁶. While these treatments have shown efficacy they have not been studied in a blinded fashion and are frequently used as a second line treatments when ACTH or vigabatrin has failed.

Topiramate has been shown in several studies to have efficacy up to 45% for the resolution of infantile spasms^{12-14, 17-19}. Most of the studies have looked at patients that have either failed

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a previous drug, such as ACTH or vigabatrin, prior to receiving topiramate¹⁷⁻²². Other studies have treated patients with multiple medications concurrent with topiramate for their infantile spasms¹³. The studies to date have suggested that topiramate is tolerated though lethargy, weight loss, anorexia, anhydrosis have been reported²¹⁻²³. Our study was focused on determining if topiramate is being used in clinical practice for the initial treatment of infantile spasms; identifying if there is a treatment bias in patient selection for ACTH or topiramate; and how often patients have resolution of both clinical spasms and hypsarrhythmic EEG following treatment.

Methods

A retrospective chart review was performed on patients diagnosed with infantile spasms between 2002 and 2005 at the Children's Hospital of Philadelphia. Fifty randomly chosen patient charts were obtained for review. Those receiving either ACTH or topiramate as the initial treatment for infantile spasms had further data analysis. Charts were screened for demographics, electroencephalographic (EEG), clinical findings, etiology, medications prescribed, doses, remission duration, treatment discontinuation due to side effects and qualitative clinical data as described. Infantile spasms remission was defined as a total cessation of both clinical and hypsarrhythmia features of infantile spasms. Presence of hypsarrhythmia and initial treatment with ACTH or topiramate was required for inclusion. Initial treatment was defined as first medication prescribed following diagnosis. Relapse was defined as recurrence either of clinical spasms and/or recurrence of the hypsarrhythmia on the EEG following a resolution of both clinical spasms and hypsarrhythmia at an office visit. Clinical data was organized in a database and quantitatively analyzed using unpaired t-test with Welch's correction and Wilcoxon analysis for the treatment duration in responders.

Results

Demographics: A total of thirty-one patients (15 males and 16 females) met inclusion criteria. All patients were younger than 21 months at the time of initial treatment. The mean age of initial treatment was 4.68 months (range, 2 to 7.5 months, median, 5 months) for ACTH and 8.05 months (range, 0 to 21 months, median, 6.0 months) for topiramate. The difference in mean age between the two initial treatment groups was statistically significant, as calculated by an unpaired t-test with Welch's correction ($P = 0.032$). Three patients from the ACTH initial treatment group and two patients from the topiramate initial treatment group had cryptogenic infantile spasms, while the remaining patients in both groups possessed a combination of genetic and clinical findings consistent with a symptomatic etiology for their infantile spasms (see Table 1 and 2). Duration of clinical spasms prior to treatment did not differ between the treatment groups. Fifteen patients exhibited flexor and four extensor spasms in the topiramate initial treatment group, while eight flexor and three extensor spasms were observed in the ACTH treatment group. For one patient, flexor versus extensor spasm activity was not recorded.

Fourteen patients were not included for further analysis. Two patients were excluded for receiving ACTH and topiramate simultaneously as their initial treatment, four for receiving vigabatrin as their first treatment, one for receiving phenobarbital and B6 as their first treatment, one for a non-hypsarrhythmic EEG, one for a change in diagnosis from infantile spasms to another condition, and five for missing pertinent chart information to confirm the diagnosis or initial treatment.

Treatment

Twelve patients were initially treated with daily ACTH and nineteen with topiramate (see Table 2). The mean highest doses were 146U/M²/day (range, 88-180 U/M²/day) of ACTH and 14.35 mg/kg per day (range, 1.3 to 35.1 mg/kg per day) of topiramate.

Outcome

Six of twelve (50%) patients treated with ACTH had resolution of their clinical spasms and hypsarrhythmic EEG within a few weeks of starting treatment. Three of the patients had a recurrence of their infantile spasms and hypsarrhythmic EEG between 2 and 6 months later. Four of the nineteen patients treated with topiramate eventually achieved resolution of their spasms and hypsarrhythmic EEG. The amount of time to achieve permanent resolution of clinical spasms and hypsarrhythmic EEG was less than one month in all the patients on ACTH alone and 19.5 months average (range, 0 to 69 months) on topiramate. Three of twelve (25%) patients treated initially with ACTH and four of nineteen (21%) treated with topiramate eventually achieved permanent infantile spasms remission (see Table 4).

Nine patients failed ACTH including three with temporary remission, all received additional treatment regimens, and four eventually achieved permanent infantile spasms remission. Seven were treated with topiramate as their second medication and one had permanent resolution of infantile spasms. Of the fifteen patients that failed topiramate initially, nine were given additional treatment for their infantile spasms, and three eventually achieved permanent infantile spasms remission. Seven of the eight were treated with ACTH as their second medication and two of the seven achieved permanent infantile spasms remission.

Side Effects

Charts were reviewed for documented side effects; only two patients initially treated with topiramate had documented side effects (appetite loss, tremors, and lethargy). In neither case did side effects result in stopping treatment. None of the patients on ACTH had documented side effects and none had premature medication withdrawal.

Discussion

Here we describe a retrospective study of patients treated for infantile spasms at the Children's Hospital of Philadelphia from 2002 to 2005. We find that topiramate was being widely used as a first line treatment for infantile spasms in a large group academic practice. Topiramate monotherapy was the most common first line treatment for infantile spasms, ACTH monotherapy second and vigabatrin third. Because of the retrospective nature of the study, likely selection biases and variability within treatment regimens the findings are best interpreted as a description of the use of ACTH and topiramate for infantile spasms in a clinical setting. We found a selection bias toward younger patients receiving ACTH treatment compared to topiramate but other parameters, such as symptomatic versus cryptogenic did not clearly stratify with treatment regimen. Most patients were symptomatic and neither, ACTH nor topiramate succeeded in the long-term resolution of clinical spasms and hypsarrhythmic EEG in the majority of patients.

The range of maximum doses of ACTH and topiramate and the corresponding titration schedules reflect the diversity of approaches reported in the literature^{12, 17, 18, 20}. Side effect reporting is limited to those the treating physician chose to document and were those previously reported for topiramate, appetite loss, tremors, and lethargy, but no patient appeared to have either medication stopped for side effects alone. There was a wide range of topiramate dosing, 1.3-35 mg/kg/day, with an average of 14mg/kg/day similar to that achieved in prior studies

11, 12. Two of the patients that responded to topiramate in 1 month or less did so at low doses, 1.3 and 3.4 mg/kg/day, raising the possibility of an extremely treatment responsive population.

The majority of patients in both treatment groups had symptomatic infantile spasms with developmental delay, abnormal neurologic exam and/or abnormal MRI findings. Only 5 out of the 32 patients were classified as cryptogenic at the time of therapy initiation. Six of the twelve patients treated with ACTH had resolution of their spasms and hypsarrhythmia within the first month of treatment but three patients had recurrence after 2, 2.5 and 6 months. The response rate to ACTH while low, is similar to other studies showing a 50% or less clinical response in symptomatic patients initially with a 20% relapse rate and only ~20-30% resolution of hypsarrhythmia on EEG^{3, 24}. The long-term efficacy of topiramate was four of nineteen lower than the 45% reported in one study, but similar to the 20% in a more recent study^{11, 12}. In addition to the reported monotherapy patients, two patients started within days on both topiramate and ACTH though neither had resolution of their spasms on this regimen. Interestingly, of those patients that failed the initial drug treatment many were crossed over from topiramate to ACTH (two of seven with eventual permanent remission) or ACTH to topiramate (one of seven with eventual permanent remission) as their second line treatment in either group. As second line treatment ACTH and topiramate had relatively similar, poor rates of infantile spasms resolution for these small groups of patients.

The major difference in use of ACTH and topiramate was a longer treatment course in the topiramate treatment group. Topiramate responders had resolution of their spasms and hypsarrhythmia, 0,1,8 and 69 months versus less than a month for every patient in the ACTH treatment group. The increased duration for topiramate treatment points to the willingness of treating physicians to extend topiramate therapy, which did not occur for ACTH treatment. Because infantile spasms are felt to be an epileptic encephalopathy, there is concern for worse cognitive and behavioral outcome following a delay in the resolution of spasms and hypsarrhythmia seen in the topiramate treatment group. Supporting this concern is the report of patients with cryptogenic infantile spasms having a better cognitive outcome following treatment with ACTH than vigabatrin²⁶.

Our findings highlight significant use of topiramate as the initial treatment strategy for infantile spasms in an academic child neurology practice. A treatment bias toward treating younger patients with ACTH and older patients with topiramate was present at our center. The patients reported here were treated prior to the recent dramatic escalation in the cost of ACTH, which may further decrease its use. In summary, neither ACTH nor topiramate was highly efficacious in our mostly symptomatic patient population but overall ACTH had a rapid resolution of spasms and hypsarrhythmia.

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Table 1**Patient demographics**

Thirty-one patients met inclusion criteria. A clinical diagnosis of spasms and an EEG report with hypsarrhythmia were both required for inclusion. The only difference we found between treatment groups was an older age at diagnosis in the topiramate treatment group. The rest of the demographics were similar between the ACTH and topiramate groups.

	Initial Treatment	
	Topiramate	ACTH
Male	8	7
Female	11	5
Average Age (months)	8.05	4.68*
Cryptogenic	2	3
Genetic	2	2
Clinical Etiology		
HIE	3	1
Stroke	1	1
TS	0	0
Neurologic Exam Abnormality	17	8
MRI Abnormality	13	6
Other Physical Abnormality	6	2
Clinical Infantile Spasms		
Average Duration Prior to Treatment	2 (<1->12months)	1.5 (<1-3 months)
Flexor	15	8
Extensor	4	3
EEG Hypsarrhythmia	19	12

Average Age at diagnosis in months; cryptogenic= a normal MRI and clinical exams at the time of diagnosis. HIE - hypoxic ischemic encephalopathy, TS-tuberous sclerosis. Other physical abnormalities= non-neurologic disorders or congenital anomalies.

* P=0.03 T-test with Welch correction.

Table 2

Initial ACTH and topiramate treatment regimens, outcomes and clinical diagnosis

HIE-hypoxic ischemic encephalopathy, HLHS-hypoplastic left heart syndrome, ARX-mutation in the Aristaless related homeobox gene, PVL-periventricular leukomalacia, CMV-cytomegalovirus, CDKL5-mutation in cyclin dependant kinase like 5 gene, IVH-intraventricular hemorrhage

Initial Treatment	Highest Dose	Spasms duration prior to treatment (months)	Time to Remission (months)	Relapse (months)	Primary Diagnosis
ACTH	160U/M ² /day	<1			Cryptogenic
ACTH	missing	1	0	2	Rett syndrome
ACTH	140U/M ² /day	1			Aicardi syndrome
ACTH	88U/M ² /day	3			Hermansky-Pudlak, HIE
ACTH	170U/M ² /day	0.5	0		Polymicrogyria
ACTH	150U/M ² /day	<1	0	2.5	Cryptogenic
ACTH	180U/M ² /day	<1	0		Cystic brain lesions
ACTH	110U/M ² /day	unknown	0		Neonatal stroke, HLHS
ACTH	150U/M ² /day	<1	0	6	Hydrocephalus
ACTH	High dose	2			ARX mutation
ACTH	130U/M2/day	1			Cryptogenic
ACTH	180U/M2/day	1.5			Hypotonia, developmental delay
Topiramate	8.1 mg/kg/day	<1			Hemimegencephaly
Topiramate	31 mg/kg/day	3			PVL
Topiramate	20-30 mg/kg/day	<1			Non-accidental trauma
Topiramate	21.8 mg/kg/day	2			Congenital CMV
Topiramate	7.2 mg/kg/day	<1	Immediate Improvement; Multiple Relapses Resolution 69		HIE
Topiramate	14.3 mg/kg/day	<1			CDKL5 mutation
Topiramate	22.5 mg/day	>12			Prenatal strokes
Topiramate	35.1 mg/kg/day	<1	Immediate Improvement Multiple Relapses		Hypotonia, developmental delay
Topiramate	15.9 mg/kg/day	<1			HIE, IVH
Topiramate	5.6 mg/kg/day	<1			Cryptogenic
Topiramate	6.3 mg/kg/day	<1			Piloocytic astrocytoma

Initial Treatment	Highest Dose	Spasms duration prior to treatment (months)	Time to Remission (months)	Relapse (months)	Primary Diagnosis
Topiramate	11.5 mg/kg/day	1			HIE
Topiramate	18 mg/kg/day	<1			Hypotonia, developmental delay
Topiramate	1.3 mg/kg/day	2	0		Cryptogenic
Topiramate	3.4 mg/kg/day	<1	1		Developmental delay, abnormal white matter
Topiramate	9.3 mg/kg/day	2			Cryptogenic
Topiramate	14.3 mg/kg/day	<1	8		Premature/meningitis/PVL
Topiramate	22.5 mg/kg/day	<1			Lisencephally
Topiramate	10 mg/kg/day				Hypotonia, developmental delay
Topiramate	20 mg/kg/day	<1			Aicardi syndrome

Table 3**Secondary treatment regimens and outcomes**

Initial Treatment	Additional Treatments	Highest Dose	Additional Treatment Prescribed (months after initial treatment)	Permanent Remission (months after initial treatment)
ACTH	Vigabatrin	157 mg/kg/day	1	1
ACTH	Topirimate, Vigabatrin	25.7 mg/kg/day, 109.6 mg/kg/day	3.5, 5	6
ACTH	Topirimate, Vigabatrin	27.9 mg/kg/day, 104.6 mg/kg/day	2, 3	
ACTH	Topirimate	30 mg/kg/day	3	
ACTH	None			
ACTH	Topirimate, Vigabatrin	46.8 mg/kg/day, 166 mg/kg/day	2.5, 5	
ACTH	None			
ACTH	None			
ACTH	Topirimate	14 mg/kg/day	6.5	
ACTH	Vigabatrin	133 mg/kg/day	20	20
ACTH	Topirimate	4.5 mg/kg/day	1	2
ACTH	Topirimate, Vigabatrin	10 mg/kg/day, 143 mg/kg/day	7, 17	
Topirimate	ACTH	220U/M ² /day	3	
Topirimate	ACTH	150U/M ² /day	3	8
Topirimate	None			
Topirimate	None			
Topirimate	None			
Topirimate	None			
Topirimate	None			
Topirimate	Ketogenic Diet		16	18
Topirimate	ACTH	260U/M ² /day	1	
Topirimate	ACTH	140U/M ² /day	0.5	
Topirimate	ACTH, Vigabatrin	80U/M ² /day, 37 mg/kg/day	1, 37	
Topirimate	None			
Topirimate	ACTH, Vigabatrin	140U/M ² /day, 18 mg/kg/day	2, 2	
Topirimate	None			
Topirimate	None			
Topirimate	ACTH	160U/M ² /day	1	3
Topirimate	None			
Topirimate	None			
Topirimate	None			
Topirimate	Vigabatrin	90 mg/kg/day	10	

Table 4

First and second drug treatment summary

Initial Treatment	Number of Patients	Mean Highest Dose	Permanent Remission on Initial Treatment	Transient Remission to Initial Treatment	Mean Time to Permanent Remission Initial Treatment (months)
ACTH	n = 12	146U/M ² /day	n = 3	n = 3	0
topiramate	n = 19	14.35 mg/kg/day	n = 4	n = 0	19.5
Second Treatment	Number of Patients	Mean Highest Dose	Permanent Remission on Second Treatment	Transient Remission to Second Treatment	Mean Time to Permanent Remission Second Treatment (months)
ACTH	n = 7	165U/M ² /day	n = 2	n = 0	3.5
topiramate	n = 7	4.5 mg/kg/day	n = 1	n = 0	1