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Original Article

Practice Experience in the Treatment of Infantile Spasms at a Tertiary Care Center

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ABSTRACT

BACKGROUND: The current treatment guidelines for treatment of infantile spasms is ambiguous regarding individuals with known etiology and is backed by limited evidence. Recently published survey data reveal diverse treatment variation for infantile spasms. We conducted a retrospective medical record review to better understand the clinical variables which affect treatment selection for new-onset infantile spasms. **METHODS:** We systematically extracted demographic data and treatment response of children with new onset infantile spasms over a 3-year period at a single institution. Treatment was divided into three groups: vigabatrin, hormone treatment, and other therapies. **RESULTS:** Our final cohort had 65 patients; 74% had a known etiology. Sixty-two percent were initially treated with vigabatrin. Other therapies were used more often in known etiology than in unknown etiology as initial treatment (40% versus 6%; $P = 0.002$). Treatment response at 3 months was not statistically different between unknown etiology and known etiology groups (71% versus 46%; $P = 0.08$). Overall, initial treatment choice was effective in 35% (23 of 65). Eighty-six percent (37 of 42) who failed the initial medication had subsequent medication trials within 3 months. **CONCLUSIONS:** Etiology was strongly associated with initial treatment choice. The variation in treatment choice at our center reflects the limited evidence derived from well-designed clinical trials.

Keywords: infantile spasms, treatment, vigabatrin, ACTH, epilepsy

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Introduction

Infantile spasms (IS) is a childhood epileptic encephalopathy which generally carries a poor prognosis. The American Academy of Neurology and Child Neurology Society practice guidelines regarding the best practice for short-term medical treatment of IS have concluded that adrenocorticotropic hormone (ACTH) is probably effective (level B), vigabatrin (VGB) is possibly effective (level C), and ACTH may be offered over VGB in cryptogenic patients to improve developmental outcome (level C). Evidence was insufficient to establish the efficacy of oral steroids, ketogenic diet, and other anticonvulsants (level U).[1] A recent survey of child neurologists in the United States revealed diverse treatment practice and found that that some physicians are choosing therapies other than ACTH or VGB in certain patient populations.[2] The practice parameter mentions little about treatment of patients with known etiology. Moreover, it does not mention further treatment choices after medication failure or in case of relapse. To understand the clinical variables which affect treatment selection, we conducted a retrospective medical record review.

Materials and Methods

The Children's Hospital of Pittsburgh of UPMC is the only tertiary care children's hospital in southwestern Pennsylvania, serving a catchment area of approximately three million people. Almost all children with newly diagnosed IS are admitted to our hospital for evaluation and treatment. Our institution employs 22 board-certified child neurologists including seven who specialize in epilepsy. Until recently, there was no consensus or institutional protocol for the treatment of IS. Treatment was chosen by an individual physician when the patient was admitted.

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During the study period, inpatient supervision time was divided such that each attending neurologist spent an average of 2-6 weeks on service per year. This gave a unique opportunity to evaluate physicians' treatment choices and short-term remission rates.

Children with IS were identified by the *International Classification of Diseases*, *Ninth Revision*, code for IS on discharge diagnosis from September 2009 to September 2012. Medical records were reviewed and data on demographics, medical history, neurological examinations, electroencephalography (EEG), neuroimaging, and treatment responses were extracted systematically. Patients with the clinical diagnosis of new onset IS and/or hypsarrhythmia or modified hypsarrhythmia on EEG were included. All patients had clinical seizures consistent with spasms and interictal EEG consistent with hypsarrhythmia or hypsarrhythmia variant. Individuals with clinical spasms in clusters without hypsarrhythmia on EEG were excluded. Patients born before January 1, 2008 were excluded, as they were unlikely to be new onset IS based on their age.

Etiology was divided into known and unknown groups. The terms "cryptogenic," "symptomatic," and "idiopathic" were avoided based on revised International League Against Epilepsy classification.[3] All patients with an unknown etiology had normal development before onset of spasms and negative standard work up. The known etiology group was further subdivided into six categories: (1) cortical malformation; (2) perinatal insult, defined as children with prematurity, neonatal seizures, and/or hypoxic-ischemic encephalopathy; (3) trisomy 21; (4) tuberous sclerosis complex; (5) other known etiologies associated with IS; and (6) known etiology not otherwise specified (NOS). Known etiology NOS was assigned to patients with clear developmental delay or abnormal neurological examination before the onset of IS and to patients with an abnormal etiologic evaluation not known to be associated with IS. Standard etiologic work up for IS at our institution includes magnetic resonance imaging brain, cerebrospinal fluid analysis, serum amino acid, urine organic acid, and chromosome and microarray analysis.

The day that the EEG confirmed the presence of hypsarrhythmia was used as the date of diagnosis. Treatment lag was defined as the interval between the onset of spasms and the initiation of IS-specific antiepileptic medication. Treatment responder was defined as resolution of clinical spasms and resolution of hypsarrhythmia within 3 months of the initial diagnosis. Any treatment started after 3 months from the diagnosis was excluded from analysis. Treatment was divided into three groups: VGB, hormone treatment, and other therapies. VGB was titrated to goal dose of 100-150 mg/kg as tolerated. Hormone treatment group included patients treated with oral steroid and ACTH. Oral steroid used was prednisolone and doses ranged from 2 to 5 mg/kg/day for 2 weeks followed by a 4- to 6-week taper. ACTH dosing was 100-150 U/m^2 for 2 weeks followed by a 4- to 6-week taper with the exception of one patient who received 50 U/m^2 for 2 weeks with subsequent taper. Other therapies included all other anticonvulsants and the ketogenic diet. The preliminary results were discussed in our divisional quality assessment meeting.

Descriptive analysis was performed with Stata software version 10 (StataCorp LP, College Station, TX). Student *t* tests were used for continuous variables, and the Pearson chi-square or Fisher exact tests were used for categorical variables. A two-sided *P* value of less than 0.05 was considered statistically significant. This study was approved by the Institutional Review Board of the Children's Hospital of Pittsburgh.

Results

Demographics

A total of 73 patients met inclusion criteria. Eight patients were excluded from analysis because of treatment at another facility (two) and insufficient follow-up data (six). The final cohort had 65 patients with 41 males (63%). Forty-eight patients (74%) had a known etiology (Table). The median age of onset was six months (range 0.5-20 months). All six patients (9%) with onset before 3 months had known etiology. Four of those six patients had cortical malformations. The six patients (9%) with onset after 12 months were also known etiology. Two patients had trisomy 21, and four patients had perinatal insult. All patients with unknown etiology presented between 4 and 8 months with the exception of one patient who presented at 3 months (Table).

TABLE.
Demographics

Total number	65	
	41 males (63%)	
Age of onset	Median 6 mo	
	(3 wk-20 mo)	
Diagnostic lag time	Median 1 mo	
	(<1 wk-11 mo)	
Known etiology	48 (74%)	
	Cortical malformations	12
	Perinatal insult	14
	Trisomy 21	5
	Tuberous sclerosis	2
	Other known etiology associated with IS: Menkes disease, ARX, KCNQ2, nonaccidental trauma, and cardiac arrest outside of neonatal period	7
	Known etiology NOS: Bilateral extra-axial CSF collections, subdural hematomas, visual impairment, genetic mutation of unknown clinical significance, and focal seizures before IS	8
Delayed Diagnosis	10 (17%)	
	Trisomy 21	3
	Cortical malformations	3
	Perinatal insult	2
	Menkes disease	1
	Unknown	1

Abbreviations:
CSF = Cerebrospinal fluid
IS = Infantile spasms
NOS = Not otherwise specified

The median diagnostic lag time was 1 month (range, <1 week-11 months), and 85% of patients were diagnosed within 1 month of spasm onset. Nine of 10 patients with delayed diagnosis had known etiology.

Initial treatment choice

The most frequently chosen initial treatment was VGB, which was used in 62% of patients, followed by other therapies in 31% and hormone treatment in 8% of patients. Initial treatment choice was strongly associated with etiology. The patients with known etiology received other therapies more often than the patients with unknown etiology (40% versus 6%; $P = 0.002$). Other therapies used included topiramate (10), valproic acid (three), zonisamide (two), levetiracetam, phenobarbital, lacosamide, clonazepam, and ketogenic diet (one each). Patients with unknown etiology received VGB in 70% of cases and hormone therapy in 24% of cases as initial therapy (Fig 1).

Short-term treatment outcome

Fifty-two percent (34 of 65) of patients achieved short-term remission within 3 months from diagnosis.