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Original Article

Infantile Spasms Respond Poorly to Topiramate

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ABSTRACT

INTRODUCTION: Infantile spasms are seizures typical of an age-related epileptic encephalopathy. Although evidence supporting topiramate for infantile spasms is lacking, many clinicians use it for this indication. The aim of this study was to determine the rate of infantile spasm remission with topiramate at our institution. A low rate of infantile spasm remission was hypothesized. **METHODS:** This was a single-center retrospective medical record review of patients treated with topiramate for infantile spasms between January 2009 and September 2013. Records were reviewed for accuracy of diagnosis and outcome. Clinical remission of infantile spasms was defined as resolution for at least 28 days at any time during treatment with topiramate. For patients with clinical remission, posttreatment electroencephalographs were reviewed to assess for electrographic remission. To assess for confounding variables affecting remission rate, demographics and outcomes were compared with patients treated with adrenocorticotropic hormone within the same period using the same criteria for remission. **RESULTS:** Three of 31 (9.7%) patients achieved clinical remission with topiramate, two of whom also experienced electrographic remission. The third patient had electrographic remission with previous adrenocorticotropic hormone treatment but infantile spasm remission only after receiving topiramate. All three of these patients experienced subsequent electroclinical relapse during topiramate therapy. Although there were no significant demographic differences between the topiramate and adrenocorticotropic hormone cohorts, more adrenocorticotropic hormone patients achieved clinical remission (9.7% versus 56%; $P < 0.001$). **DISCUSSION:** Remission of infantile spasms with topiramate was uncommon and no patient experienced persistent electroclinical remission. These findings suggest that infantile spasms respond poorly to topiramate.

Keywords: infantile spasms, West syndrome, topiramate, pediatric, epilepsy

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Introduction

Infantile spasms are seizures that are often associated with poor developmental outcome. The treatment of infantile spasms varies widely among clinicians. Only three therapies have greater than class IV evidence to support their use for infantile spasms: adrenocorticotropic hormone (ACTH), vigabatrin, and oral corticosteroids.[1,2] There is little evidence to support the use of other therapies for infantile spasms. However, in the United States, topiramate is often used by clinicians as a "first-line" treatment for infantile spasms.[3-5] In a 2012 survey of members of the Child Neurology Society, more than 20% of respondents used topiramate as a first- or second-line treatment for infantile spasms resulting from an unknown cause and more than 30% of respondents used topiramate as a first- or second-line treatment for infantile spasms resulting from a structural or metabolic cause.[5] A 2009 single-center study from a large tertiary care center found that topiramate was the most commonly used treatment for infantile spasms regardless of etiology.[4] The aim of this study was to determine the rate of infantile spasm remission with topiramate when used at Nationwide Children's Hospital. We hypothesized a low rate of infantile spasm remission with topiramate.

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Methods

In this single-center retrospective medical record review, patients were identified using an established infantile spasms registry at Nationwide Children's Hospital. This registry identified patients by electroencephalograph database review (search terms: hypsarrhythmia and infantile spasms), hospital discharge International Classification of Diseases, ninth revision, codes (345.60, 345.61), and referral to our infantile spasms program. The diagnosis of infantile spasms was confirmed after independent medical record review by two authors. Inclusion criteria included all patients with infantile spasms treated with topiramate from January 2009 to September 2013. Exclusion criteria included patients with early-onset epileptic encephalopathy (early myoclonic encephalopathy or Ohtahara syndrome); patients who started topiramate after infantile spasms onset to address other seizure types; patients that started topiramate concomitantly with ACTH, vigabatrin, or corticosteroids; and those patients whose outcome could not be determined from the medical record. Clinical remission was defined as cessation of infantile spasms for a minimum of 28 days at any time during treatment with topiramate. For patients who experienced clinical remission, posttreatment electroencephalographs were reviewed to assess for electrographic remission. The topiramate cohort was compared with all patients treated with natural gel ACTH during the same period from the same patient registry to assess patient characteristics between cohorts that might explain differences in rates of remission. The same criteria for remission were applied to the ACTH cohort. The patient characteristics and outcomes for the ACTH cohort were previously published.[6] The ACTH cohort was treated with high-dose ACTH starting at 150 IU/m^2/day (in two divided doses) with subsequent tapering. The total duration of ACTH treatment was either 4 weeks (as described by Baram and colleagues[7]) or 12 weeks (as described by Snead and colleagues[8]).

Ethics

This study was approved by the Institutional Review Board at Nationwide Children's Hospital.

Statistical analysis

All statistical analyses were completed using SAS 9.3 (SAS Institute). Continuous variables were presented using median, mean, and range. Categorical variables were presented using percentages. Given that continuous variables were not normally distributed, the Wilcoxon rank-sum test was used for comparison between cohorts. Categorical variables were compared using Pearson chi-square test or Fisher exact test as appropriate. The significance level was set at 0.05 and all tests to assess *P* values were two-sided.

Results

Demographics of patients treated with topiramate

Thirty-nine patients with infantile spasms received topiramate during the study period. Eight patients were excluded: four because topiramate was initiated concurrently with ACTH, vigabatrin, or corticosteroids; one for a diagnosis of early-onset epileptic encephalopathy; one because topiramate was used for seizures other than infantile spasms; and two because of uncertain outcome. Data for the remaining 31 patients were analyzed (Table 1). Of these patients, 71% (22/31) were male. The age of infantile spasm onset could be determined in 28 patients with a median age of 5.5 months (mean 6.9, range 1.5-29). The median duration from infantile spasms onset to treatment with topiramate in these 28 patients was 1.3 months (mean 2.3, range 0-12). Sixteen percent (5/31) of the patients had an unknown etiology and 84% (26/31) had a known etiology.

Topiramate was the initial treatment in 17 patients, the second treatment in 10 patients, the third treatment in three patients, and the fourth treatment in one patient. Topiramate was initiated at a median age of 8 months (mean 9, range 3-32). The median maximum topiramate dose achieved was 16 mg/kg/day (mean 17.3, range 4.5-60). The median age at the time of last neurological follow-up was 37 months (mean 39, range 7-84).

Rate of infantile spasms remission with topiramate

Three of 31 (9.7%) patients experienced clinical remission of infantile spasms with topiramate (Table 1). The maximum topiramate dose achieved in the three responders ranged from 25 to 28 mg/kg/day. In these three responders, topiramate was the first treatment for infantile spasms in one patient, the second treatment in one patient, and the fourth treatment in one patient. One patient had previously failed treatment with ACTH and the other had previously failed treatment with levetiracetam, vigabatrin, and ACTH. The three responders achieved clinical remission beginning 70, 20, and 14 days, respectively, after starting topiramate. Two of these three patients also had electrographic remission. One of these patients had electrographic remission with previous ACTH treatment but clinical infantile spasm remission only after receiving topiramate. All three of these patients experienced subsequent electroclinical relapse at 3.5, 12, and 4 months, respectively, after initial clinical remission with topiramate. One of these patients experienced a subsequent clinical remission while taking clobazam. Of the 28 patients who did not achieve clinical remission of infantile spasms with topiramate, 36% (10/28) had subsequent clinical remission with a different treatment (Table 1). Of these 28 nonresponders, we were able to determine the time from topiramate initiation to the time of the next alternative antiseizure medication in 26 patients (2/28 did not receive a subsequent alternative antiseizure medication): median 2.3 months (mean 2.6, range 0.5-6.5). We were able to determine the duration of topiramate treatment in 27/28 nonresponders (one patient was lost to follow-up): median 8 months (mean 15, range 0.5-50.5), including six patients who continued to be on topiramate at the time of last neurological follow-up.

Rate of infantile spasms remission compared with ACTH

To assess for confounding variables that may affect the rate of infantile spasm remission, demographics and outcomes were compared with a cohort of patients treated with ACTH within the same period using the same remission criteria. Twenty-three of 41 (56%) patients treated with ACTH achieved infantile spasm remission. The rate of confirmed electroclinical remission was 54% (21/39) because two patients did not have electroencephalograph data after ACTH treatment. No statistically significant differences between the topiramate and ACTH cohorts were identified that would explain the significantly better response to ACTH compared with topiramate aside from the treatment itself (Table 2).