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Original Article

Effects of Topiramate on Language Functions in Newly Diagnosed Pediatric Epileptic Patients

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ABSTRACT

BACKGROUND: The aim of this study was to characterize the effects of topiramate on language functions in newly diagnosed pediatric epileptic patients. **METHODS:** Thirty-eight newly diagnosed epileptic patients were assessed using standard language tests. Data were collected before and after beginning topiramate during which time a monotherapy treatment regimen was maintained. Language tests included the Test of Language Problem Solving Abilities, a Korean version of the Peabody Picture Vocabulary Test. We used language tests in the Korean version because all the patients were spoken Korean exclusively in their families. **RESULTS:** All the language parameters of Test of Language Problem Solving Abilities worsened after initiation of topiramate (determine cause, 13.2 ± 4.8 to 11.2 ± 4.3; problem solving, 14.8 ± 6.0 to 12.8 ± 5.0; predicting, 9.8 ± 3.6 to 8.8 ± 4.6). Patients given topiramate exhibited a shortened mean length of utterance in words during response (determine cause, 4.8 ± 0.9 to 4.3 ± 0.7; making inference, 4.5 ± 0.8 to 4.1 ± 1.1; predicting, 5.2 ± 1.0 to 4.7 ± 0.6; $P < 0.05$), provided ambiguous answers during the testing, exhibited difficulty in selecting appropriate words, took more time to provide answers, and used incorrect grammar. However, there were no statistically significant changes in the receptive language of patients after taking topiramate (95.4 ± 20.4 to 100.8 ± 19.1). **CONCLUSIONS:** Our data suggest that topiramate may have negative effects on problem-solving abilities in children. We recommend performing language tests should be considered in children being treated with topiramate.

Keywords: topiramate, epilepsy, children, language function

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Introduction

Epilepsy is one of the most prevalent pediatric neurological disorders and is associated with various cognitive impairments including developmental language disorders.

Anticonvulsants are the first choice of treatment for epilepsy. The selection of an anticonvulsant according to seizure type and patient age is an important factor defining treatment outcomes. In spite of appropriate drug selection, anticonvulsant drugs may aggravate epilepsy and adversely influence development with respect to language and cognitive function. Thus treatment of epilepsy with anticonvulsant drugs requires careful monitoring of associated neuropsychiatric disorders, language development, and cognitive functioning.

Additional anticonvulsants for the treatment of epilepsy in children were developed to minimize its adverse effect compared with classic antiepileptic drugs. However, the different pharmacodynamics and pharmacokinetics in pediatric patients can cause substantial variations in drug responses compared with adult patients and lead to unexpected adverse effects, further highlighting the need for careful monitoring of pediatric epilepsy patients during the medication period.

Topiramate (TPM) was discovered in 1979 and was derived from sulfamate fructopyranose related to monosaccharide D-fructose.[1,2] Patients with various seizure types treated with TPM have demonstrated a good treatment response and have had few side effects compared with those treated with classical antiepileptic drugs.[3,4] However, several recent reports suggest that TPM is associated with

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various side effects such as weight loss, hyperthermia, drowsiness, hypohydrosis, behavior disturbances, and language and cognition disturbances.[5-7] In addition, Wheeler[8] observed that 7.2% of patients treated with TPM develop word-finding difficulties, whereas Blum et al.[9] observed that individuals treated with TPM had worse performance compared with those treated with lamotrigine for the individual comparative examinations such as the Controlled Oral Word Association test, the Symbol Digit Modalities test, and the Performance-On-Line test simulating driving skills. Lee et al.[10] investigated possible cognitive effects before and after administration of TPM and reported poor verbal fluency, attention and/or concentration, processing speed, perception, and working memory activities after TPM therapy. Most of the studies concerning the effects of TPM on cognitive function have been limited to adult epilepsy patients. Thus, in this study, we evaluated language and problem-solving skills in newly diagnosed pediatric patients undergoing TPM monotherapy, focusing especially on discourse and pragmatics.

Patients and Methods

Patients

Thirty-eight newly diagnosed pediatric patients at the Department of Pediatrics of Chonbuk National University hospital from May, 2006 to May, 2012 were evaluated by several standard language tests before and after initiation of TPM monotherapy. Comparative analysis was conducted with a control group of 30 school-aged children residing in the same area (Chonbuk) who had no medical or medication history that might have influenced their language development or cognitive function.

Methods

Topiramate therapy was initiated at a dose of 1 mg/kg/day (up to 25 mg/day) for the first 1-2 weeks and slowly increased thereafter in 2-week intervals until reaching a maintenance dose of 5 mg/kg/day or 200 mg/day (mean dosage, 4.5 mg/kg/day). Standard language tests were used as a parameter to evaluate the experimental group before TPM treatment and after titration of the medication (average period, 3 months). We used language tests in Korean version because all the patients were spoken Korean exclusively in their families.

Language tests

Test of Language Problem Solving Abilities

"Test of Language Problem Solving Abilities (TOPS)" is an evaluation tool that measures metalinguistic skills of transforming logical thinking to language in children between the ages of 5 and 12 years. The illustrations used in this study were developed by the Seoul Community Rehabilitation Center, Republic of Korea.[11]

A total of 17 illustrated materials are used for TOPS, which is divided into three categories. The first category consists of 18 questions about determining cause, including interrogative, "Why" questions (determining cause). The second category consists of 20 questions about making inferences, including "How" questions (making inferences). Finally, the third category consists of 12 questions about making predictions, including answers to questions such as "How do you know?" and "What happens?" (making prediction). Scores ranging from 0 to 2 were assigned depending on responses to each category, with a top score of 100. Answers of pediatric patients were recorded and documented immediately after the tests were completed. Scores were defined as raw scores, mean scores, and total scores for each category. The length of articulation for each answer was compared using the mean length of utterance in words (MLU-w), which defines a mean score of the length of articulation obtained by adding all the words in the answer and then dividing by the number of sentences included in the answer.

Peabody Picture Vocabulary Test

Peabody Picture Vocabulary Test (PPVT-K) is a standardized test that is approved for evaluation of receptive vocabulary development skills and is applicable to children from 2 years and 2 months old to 40 years and 11 months old.[12] The illustrations used in this study were excerpted from published material from the American Guidance Service. Raw scores were calculated based on basal and ceiling results, and equivalent ages were also measured.[12]

Statistical analysis

Statistical significance was determined using SPSS 12.0 for windows. Independent *t* tests were used to compare differences between control groups and epileptic patients before taking TPM. Paired *t* tests were used to compare differences before and after TPM monotherapy.

Results

Characteristics of the patients

This study included 38 newly diagnosed pediatric epileptic patients (male:female = 19:19; mean age, 10 ± 2 years and 8 months old) receiving monotherapy with TPM. Patients did not change drugs, were not subjected to polytherapy, and completed follow-up language tests during the study period. The study included 34 patients with complex partial seizure including five benign childhood epilepsy with centrotemporal spikes, two patients with simple partial seizures, and two patients with idiopathic generalized epilepsy. The mean age of the control group was 10 ± 2 years 8 months. The entire experimental group had partial seizures and had no significant findings on brain magnetic resonance imaging.

Results of the TOPS

Comparison of TOPS for questions belonging to the "determine cause" category

The highest score in the "determine cause" category was 36. A mean score of 13.2 ± 4.8 was obtained for pediatric epileptic patients before TPM treatment, which decreased to 11.2 ± 4.3 after taking TPM, the difference of which was statistically significant (Table 1; Fig 1; $P < 0.05$).

In terms of linguistic representation skill before taking TPM, children were able to list more than two appropriate contents with a specific reason, explain results to "Why" questions, and use more than two subjects and associated predicates. However, after TPM monotherapy, the same children expressed answers more ambiguously and less specifically in only one word and sometimes suggested

TABLE 1.
Changes of the Test of Language Problem Solving Abilities Scores After Topiramate Initiation

	Pre-TPM	On-TPM	Control
Determine cause	13.2 ± 4.8	$11.2 \pm 4.3^{*}$	14.4 ± 2.5
Making inferences	14.8 ± 6.0	12.8 ± 5.0	15.2 ± 3.7
Predicting	9.8 ± 3.6	8.8 ± 4.6	9.9 ± 3.0
Total	37.8 ± 13.3	32.8 ± 13.1	39.6 ± 9.0

Abbreviations:
On-TPM = After topiramate medication
Pre-TPM = Before topiramate medication.
* $P < 0.05$