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# Influence of valproate on language functions in children with epilepsy

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ABSTRACT

The aim of the current study was to assess the influences of valproate (VPA) on the language functions in newly diagnosed pediatric patients with epilepsy. We reviewed medical records of 53 newly diagnosed patients with epilepsy, who were being treated with VPA monotherapy (n = 53; 22 male patients and 31 female patients). The subjects underwent standardized language tests, at least twice, before and after the initiation of VPA. The standardized language tests used were *The Test of Language Problem Solving Abilities*, a Korean version of *The Expressive/Receptive Language Function Test*, and the *Urimal Test of Articulation and Phonology*. Since all the patients analyzed spoke Korean as their first language, we used Korean language tests to reduce the bias within the data. All the language parameters of the *Test of Language Problem Solving Abilities* slightly improved after the initiation of VPA in the 53 pediatric patients with epilepsy (mean age: 11.6 ± 3.2 years), but only "prediction" was statistically significant (determining cause, 14.9 ± 5.1 to 15.5 ± 4.3; making inference, 16.1 ± 5.8 to 16.9 ± 5.6; prediction, 11.1 ± 4.9 to 11.9 ± 4.2; total score of TOPS, 42.0 ± 14.4 to 44.2 ± 12.5). The patients treated with VPA also exhibited a small extension in mean length of utterance in words (MLU-w) when responding, but this was not statistically significant (determining cause, 5.4 ± 2.0 to 5.7 ± 1.6; making inference, 5.8 ± 2.2 to 6.0 ± 1.8; prediction, 5.9 ± 2.5 to 5.9 ± 2.1; total, 5.7 ± 2.1 to 5.9 ± 1.7). The administration of VPA led to a slight, but not statistically significant, improvement in the receptive language function (range: 144.7 ± 41.1 to 148.2 ± 39.7). Finally, there were no statistically significant changes in the percentage of articulation performance after taking VPA. Therefore, our data suggested that VPA did not have negative impact on the language function, but rather slightly improved problem-solving abilities.



## 1. Introduction

Patients with epilepsy, which is a well-known disorder, may have cognitive impairments, including deficits in the language functions. Language impairment in patients with epilepsy are associated with the type of epilepsy, age of onset, duration of epilepsy, frequency of seizures, and antiepileptic drugs (AEDs) [1–3].

Although AEDs are the treatment of choice for epilepsy, some of them are well known to aggravate language function [4–8]. The adverse effects of AEDs on cognitive function depend on the number of drugs, type, dosage, and duration [9–12]. Severe linguistic adverse effects are one of the reasons AEDs are frequently discontinued [13,14]. Therefore, when prescribing AED treatment, physicians should carefully observe the patient's cognitive ability and language development, especially in the pediatric age group.

New AEDs, with fewer adverse drug reactions such as neuropsychological, gastrointestinal, dermatological, hematological, and other effects were developed in the last few decades [15]. However, given their effectiveness and cost-benefit, classic AEDs are still used for epilepsy.

Valproate (VPA) is one of the classic AEDs, which is widely used to treat generalized and focal epilepsy. It increases the level of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), in the brain, and enhances the action of GABA at the postsynaptic receptor [16,17]. Several authors reported that VPA is associated with various adverse effects, such as nausea, headache, prolonged bleeding time, thrombocytopenia, tremor, alopecia, asthenia, infection, somnolence, and hepatic toxicity [18–21]. However, VPA is known to have little adverse effect on cognitive function, including language function, when compared with other classical AEDs, such as phenobarbital (PB), phenytoin, and carbamazepine. Donati et al. [22] reported that VPA, carbamazepine, and oxcarbazepine monotherapy, prescribed to newly diagnosed children and adolescents with focal seizures, had no impact on their cognitive function. Further, Sun et al. [23] reported that VPA and topiramate monotherapy had little impact on cognitive function. However, Masur et al. [24] reported that VPA worsened attention compared with ethosuximide and lamotrigine in children with newly

*Abbreviations:* AEDs, antiepileptic drugs; MLU-w, mean length of utterance in words; PB, phenobarbital; REVT, Receptive & Expressive vocabulary test; SD, standard deviation; TOPS, Test of Language Problem Solving Abilities; U-TAP, Urimal test of articulation and phonology, Urimal means Korean language; VPA, valproate.

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diagnosed childhood absence epilepsy. Therefore, despite the majority of studies showing that VPA does not adversely affect cognitive function, the impact on cognitive function is still controversial.

We evaluated the language problem-solving abilities, and receptive and expressive vocabulary in newly diagnosed pediatric patients undergoing VPA monotherapy for the reaffirmation of the safety profile, in relation to language development.

## 2. Material and methods

### 2.1. Patients

A total of 71 newly diagnosed pediatric patients with epilepsy in the Department of Pediatrics of Chonbuk National University Hospital were recruited for the current study. All patients started treatment with VPA alone, which they maintained, until at least the second set of language tests was performed. We performed standardized tests on these patients, which covered all important aspects of speech and language processing. Initial language data were collected right before the VPA treatment was initiated. VPA monotherapy was then maintained for at least 1 month until the second set of tests was performed. The follow-up data, which were collected, were then compared and evaluated against the initial data.

Of the 71 patients who were recruited for this study, 18 patients had to be excluded for the following reasons: a test interval of over 12 months (7 patients), lack of data (9 patients), and overly abnormal result between initial and follow-up tests (2 patients). Thus, a total of 53 patients were included in the current study. A comparative analysis was also conducted with a control group of 50 school-aged children residing in the same province, with no medical or treatment history, which could have affected their language function.

### 2.2. Methods

The current study is a retrospective chart review of prospectively collected data, including the type of epilepsy, demographic findings, and the result of the language function test.

The VPA therapy was initiated at a dose of 10 mg/kg/day (maximum dose: 250 mg/day), which was then slowly titrated up to 30 mg/kg/day, as required, over 1–2 weeks (maximum daily dose: 1000 mg/day). The language function of the experimental cohort was assessed using three kinds of Korean language tests, at time points before initiating VPA treatment, and after the titration of the medication. The interval of first to second test was within 2–12 months (average period: 3.9 months). There was no recurring epileptic seizure between tests. However, after the second language test, only 1 patient had recurring epileptic seizure, which led to change from VPA to other AEDs.

### 2.3. Language tests

#### 2.3.1. Test of Language Problem Solving Abilities (TOPS) and the mean length of the utterance of words (MLU-w)

The TOPS is a test that measures metalinguistic skills of transforming logical thinking to language during the ages within 5–12 years. The patients answered each question presented in the illustrations below (Fig. 1, Table 1). The illustrations, which were used in the current study, were developed by the Seoul Community Rehabilitation Center, Republic of Korea [25]. The test contained 17 illustrations, which were divided into three groups, i.e., determining cause, and making inference, and prediction. The "determining cause" category consisted of 18 questions, including "Why" questions. The "making inference" category consisted of 20 questions related to "How" questions. The "prediction" category consisted of 12 questions, like "How do you know?" and "What happens?" (Table 1). The answers of pediatric patients were recorded and documented during the time of testing. Scores ranging from 0 to 2 were assigned, depending on the response to each category. Scores were defined as raw scores, mean scores, and total scores for each category.

**Fig. 1.** Test of language problem solving.

The length of articulation for each answer of the TOPS was measured using the MLU-w, which defined a mean score of the length of articulation obtained by adding all the words in the answer and then dividing them by the number of sentences included in the answer (Table 1).

#### 2.3.2. Receptive & Expressive vocabulary test (REVT)

The REVT measures receptive and expressive vocabulary development, from the age of 2 years to adulthood. The REVT was developed by the Korean Journal of Communication Disorders. During the receptive skill test, participants were asked to select one of four pictures corresponding to the target vocabulary; during the expressive skill test, participants had to express vocabulary to the presented pictures (Fig. 2A, B).

#### 2.3.3. Urimal test of articulation and phonology, Urimal means Korean language (U-TAP)

The U-TAP is a standardized tool that is used to evaluate the patient's articulation ability, in correlation to their age. The test identifies the weak points of phonation. The test can test children aged 2–12 years. The tester presents a certain picture to the children and leads them to make a sentence, which includes a targeted phoneme. The target phonemes include 19 consonants and 10 vowels. The accuracy is calculated by dividing the number of incorrect phonemes by the total number of phonemes, and is expressed as the correct percentage.

### 2.4. Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 21.0 for windows. An independent *t*-test was used to compare the differences between the subject and control groups. Paired *t*-tests were used to compare the differences before and after VPA monotherapy. All values were expressed as mean ± standard deviation (SD). Statistical significance was set at $P < 0.05$.

## 3. Results

### 3.1. Patient characteristics

The mean age of the patient cohort was 11.6 ± 3.2 years (male:female patients = 22:31). During this study, the patients did not change the type of drug they were taking, nor did they add other AEDs. They also completed all follow-up language tests during the study period. In the study cohort, 46 patients had generalized seizures, including 13 patients with epilepsy with generalized tonic–clonic seizure alone, 12 patients with childhood absence seizure, 14 patients with juvenile absence seizure, and seven patients with juvenile myoclonic