



The relation between antiepileptic drug type and cognitive functions in childhood epilepsy: A prospective observational study

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ABSTRACT

Aim: This study investigated the effect of antiepileptic drug monotherapy on cognitive functions in pediatric epilepsy patients.

Methods: 98 recently diagnosed epilepsy patients aged 6-16 years were included. All patients underwent routine laboratory tests, electroencephalography, brain magnetic resonance imaging, and intelligence testing. The patients were treated with valproic acid (VA), carbamazepine (CBZ), oxcarbazepine (OXC), or levetiracetam (LEV). The Wechsler Intelligence Scale for Children (WISC-R) was applied three times, before, six months and 12 months after the start of antiepileptic therapy.

Results: No significant difference was determined among the mean verbal, performance and total intelligence scores of patients using a single antiepileptic drug at baseline, after six or 12 months.

Conclusion: We conclude that the type of antiepileptic drug using has no adverse effects on cognitive functions.

Keywords: Epilepsy, antiepileptic drugs, cognitive functions, WISC-R, childhood.

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Introduction

Epilepsy is the most common chronic, recurring neurological disease in childhood, and is an important public health problem [1,2]. Learning problems and low academic

performance are the significant effects of epilepsy [3,4]. The primary aim of antiepileptic drugs for treatment of epilepsy is seizure control, and the secondary objective is to prevent cognitive disorders, thus avoiding potential future poor academic performance [5]. Antiepileptic drugs have both positive and adverse effects on cognitive functions, and these must be taken into account in the selection of anti-epileptics [1,3]. Various studies have reported that antiepileptic drugs impair cognitive functions in children [6-13], while other comparative studies have reported

no adverse effects of antiepileptic drug types on these functions [14-18]. However, there have been a few previous comparative, long-term studies in children showing the effects on cognitive functions of antiepileptic such as valproic acid, carbamazepine, oxcarbazepine, and levetiracetam that are frequently today. This study investigated and compared the effects on cognitive functions of antiepileptic medications.

Methods

The study was performed between November 2009 and June 2011 at the Erciyes University Medical Faculty Pediatric Neurology Department, Turkey. Approval for the study was granted by the Erciyes University Medical Faculty Ethical Committee (Decision no: 08/112). Informed consent forms were obtained from patients' parents. Ninety-eight newly diagnosed epilepsy patients in the 6-16 age group, with no visual, hearing or speech problems, capable of reading and writing, with no other chronic disease and started on antiepileptic monotherapy any one of; valproic acid (VA) (20-30mg/kg/d), carbamazepine (CBZ) (20-25mg/kg/d), oxcarbazepine (OXC) (20-25mg/kg/d), or levetiracetam (LEV) (30-40mg/kg/d) were included in the study. Patients aged 6-16 years diagnosed with epilepsy characterized by generalized tonic-clonic seizures or partial-onset seizures with or without secondary generalization were eligible. The diagnosis of epilepsy was based on clinical and electroencephalography (EEG) findings by two different pediatric neurologists according to the International League Against Epilepsy (ILAE) classification [19]. Before the initiation of antiepileptic therapy, all 98 patients underwent routine laboratory tests, EEG, brain magnetic resonance imaging (MRI), and intelligence testing.

Exclusion criteria included (1) signs of progressive neurodegenerative and metabolic disorders, (2) a history of major psychiatric disorders, (3) a history of alcohol or drug abuse, (4) a chronic medical illness, (5) ongoing use of any medication affecting the central nervous system, (6) a history of head injury with loss of consciousness, (7) visual or hearing disorders (8) previous exposure to any AED, (9) in whom seizure control had not been achieved, using more than one antiepileptic medications, (10) not attending regular follow-up, and (11) older than 16 years old.

Sociodemographic data forms were completed with the relatives of all patients enrolled. The Wechsler Intelligence Scale for Children (WISC-R) was applied three times in the evaluation of patients' cognitive functions, at time of presentation before starting antiepileptic drugs, and after six and 12 months starting of antiepileptic use. We also inquired into seizure control.

Wechsler Intelligence Scale for Children (WISC-R)

WISC-R is one of the tests frequently used in research and to measure intelligence. The inclusion of examples from various skill areas in the subtests, the precision of the scoring and interpretation bases, and the satisfactory nature of the psychometric characteristics all contribute to the popularity of the scale. The Turkish-language standardization of the WISC-R meets the need for tests aimed at children [20].

Statistical Analysis

The data obtained were analyzed on SPSS 15.0 for Windows software. Parametric statistical analysis methods were employed due to the adequate numbers of subjects and controls and to values being normally distributed.

Compatibility with normal distribution of quantitative data was assessed using the Kolmogorov-Smirnov normality analysis test. Normally distributed data were expressed as mean±standard deviation. Variation between drugs was analyzed using one-way ANOVA. The Scheffe procedure was used to identify the group representing the source of difference. Variation between two time periods (0, 6 and 12 months) was examined using the Paired-t test, while variation among more than two time points was analyzed using Repeated Measures Analysis. The Bonferroni test was employed post hoc. Non-normally distributed data were expressed as median, and min-max. Variation between groups was evaluated using Kruskal-Wallis Analysis of Variance. The Bonferroni-corrected Mann Whitney U test was used to identify the group representing the source of difference. Variation between more than two time points was analyzed using the Friedman test. The Wilcoxon rank test with Bonferroni correction was employed to identify which group was different. Qualitative data were expressed as %. Variation between groups was analyzed using the Chi-Square test. 0.05 was regarded as representing statistical significance.

Results

Evaluation of gender and mean ages by medications is shown in Table 1, and mean verbal, performance and total intelligence scores in Table 2. The patients consisted of 53 (54 %) boys and 45 (46 %) girls. Patients' ages ranged between six and 16 years. The age for VA, CBZ, OXC and LEV cure groups was 10.7±2.6, 11.5±2.8, 10.5±2.6 and 10.5±2.6, respectively.

Mean verbal, performance and total intelligence scores were 91.3, 93.4 and 92.3 in girls and 90.5, 93.2 and 91.85 in boys,

respectively. Three patients were excluded since seizure control could not be achieved at the end of six months. One patient was started on a second antiepileptic since seizure control could not be achieved at the end of 12 months, and two patients were excluded for discontinuing medication of their own volition. The study was thus completed with 92 patients. Brain MRI was performed in all patients and MRI results were pathological in 7 patients (arachnoid cyst, nonspecific white matter lesions). 68 patients had generalize tonic clonic (GTC), 3 had juvenile absans type and 21 had focal seizures.

Discussion

No significant difference was observed in terms of cognitive functions between male and female patients using single antiepileptic. When valproic acid, carbamazepine, oxcarbazepine, and levetiracetam were compared among themselves and with baseline and six- and 12-month data, we again observed no significant variation between drug type and time points, and no adverse effects on cognitive functions.

Malbourne and et al. [16] conducted a case-control study of 33 Jamaican children with uncomplicated epilepsy and 33 of their classmates matched for age and gender to determine whether epilepsy resulted in differences in cognitive ability and school achievement and if socioeconomic status or the environment had a moderating effect on any differences. Intelligence, language, memory, attention, executive function, and mathematics ability were assessed using selected tests from NEPSY, WISC-R, TeaCh, WRAT3 - expanded, and Raven's Coloured Progressive Matrices. They found that there was no significant difference in IQ, children with epilepsy and their controls. This study was conducted

Table 1. Gender and mean age distributions by medications.

Parameters	VA (%)	CBZ (%)	OXC (%)	LEV (%)
Sex Female	19 (19.4)	5 (5.1)	12 (12.2)	9 (9.2)
Male	21 (21.4)	8 (8.2)	13 (13.3)	11 (11.2)
Total	40 (40.8)	13 (13.3)	25 (25.5)	20 (20.4)

VA: Valproic acid, CBZ: Carbamazepine, OXC: Oxcarbazepine, LEV: Levetiracetam.

Table 2. Mean verbal, performance and total intelligence scores by medications.

Medication	N	Scores	Month 0	Month 6	Month 12	<i>p</i>
VA	37	Verbal Intelligence	91.7±13.8	90.4±12.6	90.7±17.8	0.60
		Performance Intelligence	94.4±16.5	96.4±16.3	97.8±16.3	0.30
		Total Intelligence	92.4±15.0	92.8±14.4	93.7±17.2	0.74
CBZ	13	Verbal Intelligence	94±14.7	93.9±14.3	93.6±16.5	0.98
		Performance Intelligence	97.2±13.4	96.6±14.5	96.3±18.8	0.90
		Total Intelligence	95.2±14.3	94.9±14.8	94.5±18.8	0.92
OXC	23	Verbal Intelligence	95.2±14.5	96.4±14.2	97.7±13.6	0.27
		Performance Intelligence	95.9±13.6	95.4±12.8	97.9±15.0	0.09
		Total Intelligence	95.1±14.6	95.7±13.6	97.6±14.2	0.32
LEV	19	Verbal Intelligence	90.8±15.7	92.4±13.4	89.3±15.1	0.17
		Performance Intelligence	93.1±14.0	94.2±13.4	91.05±14.2	0.31
		Total Intelligence	91.3±14.8	92.8±13.6	89.2±14.5	0.12

VA: Valproic acid, CBZ: Carbamazepine, OXC: Oxcarbazepine, LEV: Levetiracetam.

without regard to the antiepileptic drugs used and there was no difference in the IQ comparison as in our study.

In Taylor et al.'s [17] Standard and New Antiepileptic Drugs (SANAD) multi-center, randomized clinical study involving standard antiepileptic medications (carbamazepine and valproate) and novel antiepileptic (gabapentin, lamotrigine, oxcarbazepine and topiramate), 222 epileptic patients underwent psychometric evaluation at three and 12 months, and no cognitive impairment was determined. However, the authors also reported a number of limitations, such as the lack of a control group, the heterogeneous nature of the study group, and that only 23% completed neuropsychological tests. Similarly to that study, we enrolled patients using the standard antiepileptic valproic acid and carbamazepine and the new antiepileptic oxcarbazepine and levetiracetam, and determined no significant difference in intelligence scores after six and 12 months. Particular strengths of our study are that 91% of patients completed it and the homogeneous nature of the study group. Its limitations include the absence of a control group and a monitoring period of 12 months.

In their prospective cohort study in which 407 patients were monitored for 15 years, Sogawa et al. [18] compared patients with single unprovoked seizures with other epilepsy patients and reported only minimal long-term effects on educational cognitive activities. In this study, patients with seizure control established by a single antiepileptic drug were not compared with other epilepsy patients. The absence of impairment of cognitive functions in our single seizure patients may be linked to establishment of complete seizure control.

The cognitive effects of topiramate and levetiracetam were compared in newly diagnosed epilepsy patients in another study

[21]. Cognitive complaints are common in topiramate treatment and frequently lead to drug withdrawal. The impact of levetiracetam on cognitive function is only mild. The difference in neurocognitive complaints was not statistically significant. Patients using topiramate were not included in our study, since it is not employed long term in our clinic due to its side-effects in children with epilepsy. No significant difference was determined when the cognitive effects of oxcarbazepine were compared with those of valproic acid, carbamazepine and levetiracetam in this study. In agreement with our study, another study investigating the cognitive effects of oxcarbazepine observed no significant effect on cognitive functions of one-year oxcarbazepine use [22].

Our findings were similar to those of another study reporting no significant adverse effect on cognitive functions at the end of one-year levetiracetam therapy [23]. However, the patients in our study were monitored, 12 months, at the end of which we observed no impact on cognitive functions.

A Randomized, double-blind, placebo-controlled study showed positive effects in cognitive functions in epileptic children treatment with levetiracetam [24].

Our study include the lack of a control group, the follow-up period of 12 months, and that it was not multi-center research with a larger number of patients. A secondary limitation is that tests that can be used to assess cognitive functions have a number of difficulties in terms of reliability and applicability in Turkey. Moreover, there have been few comprehensive studies involving the antiepileptic drugs we commonly use and assessing cognitive functions in children. It is essential to consider how cognitive functions and academic performance may be affected when selecting

drugs for use in children with epilepsy. It is important to ensure that the antiepileptic that we determine will best achieve seizure control is also a medication that has a positive effect, or no adverse impact, on cognitive functions. We observed that the antiepileptic agents we frequently employ have no adverse impact on cognitive functions. However, further longer-term and comprehensive are now required on this subject.

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References

- [1]Helmstaedter C, Schoof K, Rossmann T, Reuner G, Karlmeier A, Kurlmann G. Introduction and first validation of EpiTrack Junior, a screening tool for the assessment of cognitive side effects of antiepileptic medication on attention and executive functions in children and adolescents with epilepsy. *Epilepsy Behav.* 2010; 19(1): 55-64.
- [2]Neubauer BA. Cognition and behavior in childhood epilepsy. *Neuropediatrics.* 2018; 49(01):082.
- [3]Vinayan KP. Epilepsy, antiepileptic drugs and educational problems. *Indian Pediatr.* 2006; 43(9): 786-94.
- [4]Dunn DW. Neuropsychiatric aspects of epilepsy in children. *Epilepsy Behav.* 2003; 4(2): 101-6.
- [5]Moavero R, Santarone ME, Galasso C, Curatolo P. Cognitive and behavioral effects of new antiepileptic drugs in pediatric epilepsy. *Brain Dev.* 2017; 39(6): 464-69.
- [6]Camfield CS, Chaplin S, Doyle AB, Shapiro SH, Cummings C, Camfield PR. Side effects of phenobarbital in toddlers; behavioral and cognitive aspects. *J Pediatr.* 1979; 95(3): 361-65.
- [7]Vining EP, Mellitis ED, Dorsen MM, Cataldo MF, Quaskey SA, Spielberg SP, et al. Psychologic and behavioral effects of antiepileptic drugs in children: a double-blind comparison between phenobarbital and valproic acid. *Pediatrics.* 1987; 80(2): 165-74.
- [8]Calandre EP, Dominguez-Granados R, Gomez-Rubio M, Molina-Font JA. Cognitive effects of long-term treatment with phenobarbital and valproic acid in school children. *Acta Neurol Scand.* 1990; 81(6): 504-6.
- [9]Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures--effects on intelligence and on seizure recurrence. *N Engl J Med.* 1990; 322(6): 364-69.
- [10]Sabers A, Møller A, Dam M, Smed A, Arlien-Søborg P, Buchman J, Andersen EB, Boesen F, Dam AM, Lyon BB, et al. Cognitive function and anticonvulsant therapy: effect of monotherapy in epilepsy. *Acta Neurol Scand.* 1995; 92(1): 19-27.
- [11]Seidel WT, Mitchell WG. Cognitive and behavioral effects of carbamazepine in children: data from benign rolandic epilepsy. *J Child Neurol.* 1999; 14(11): 716-23.
- [12]Stores G, Williams PL, Styles E, Zaiwalla Z. Psychological effects of sodium

- valproate and carbamazepine in epilepsy. *Arch Dis Child*. 1992; 67(11): 1330-7.
- [13] Blennow G, Heijbel J, Sandstedt P, Tonny B. Discontinuation of antiepileptic drugs in children who have outgrown epilepsy: effects on cognitive function. *Epilepsia*. 1990; 31 Suppl 4: S50-3.
- [14] Chen Y, Chi Chow J, Lee I. Comparison the cognitive effect of anti-epileptic drugs in seizure-free children with epilepsy before and after drug withdrawal. *Epilepsy Res*. 2001; 44(1): 65-70.
- [15] Chen YJ, Kang WM, So WC. Comparison of antiepileptic drugs on cognitive function in newly diagnosed epileptic children: a psychometric and neurophysiological study. *Epilepsia*. 1996; 37(1): 81-86.
- [16] Melbourne Chambers R, Morrison-Levy N, Chang S, Tapper J, Walker S, Tulloch-Reid M. Cognition, academic achievement, and epilepsy in school-age children: a case-control study in a developing country. *Epilepsy Behav*. 2014; 33:39-44.
- [17] Taylor J, Baker GA, Jacoby A. Levels of epilepsy stigma in an incident population and associated factors. *Epilepsy Behav*. 2011; 21(3):255-60.
- [18] Sogawa Y, Masur D, O'Dell C, Moshe SL, Shinnar S. Cognitive outcomes in children who present with a first unprovoked seizure. *Epilepsia*. 2010; 51(12):2432-39.
- [19] Falco-Walter JJ, Scheffer IE, Fisher RS. The new definition and classification of seizures and epilepsy. *Epilepsy Res*. 2018; 139: 73-79.
- [20] Wechsler D. *Manual for the Wechsler Intelligence Scale for Children-Revised*. New York: The Psychological Corporation. 1974.
- [21] Bootsma HP, Aldenkamp AP, Diepman L, Hulsman J, Lambrechts D, Leenen L, Majoie M, Schellekens A, de Krom M. The Effect of Antiepileptic Drugs on Cognition: Patient Perceived Cognitive Problems of Topiramate versus Levetiracetam in Clinical Practice. *Epilepsia*. 2006; 47 Suppl 2:24-27.
- [22] Kim D, Seo JH, Joo EY, Lee HW, Shin WC, Hong SB. Cognitive and psychosocial effects of oxcarbazepine monotherapy in newly diagnosed partial epilepsy. *Clin Neuropharmacol*. 2014; 37(4):100-7.
- [23] Mandelbaum DE, Bunch M, Kugler SL, Venkatasubramanian A, Wollack JB. Efficacy of levetiracetam at 12 months in children classified by seizure type, cognitive status, and previous anticonvulsant drug use. *J Child Neurol*. 2005; 20(7):590-94.
- [24] Levisohn PM, Mintz M, Hunter SJ, Yang H, Jones J; N01103 Levetiracetam Study Group. Neurocognitive effects of adjunctive levetiracetam in children with partial-onset seizures: a randomized, double-blind, placebo-controlled, noninferiority trial. *Epilepsia*. 2009; 50(11):2377-89.