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EVALUATION OF COGNITIVE FUNCTIONS OF THE CHILDREN WITH EPILEPSY TREATED WITH CARBAMAZEPINE

KARBAMAZEPİN TEDAVİSİ ALAN EPİLEPSİLİ ÇOCUKLARIN BİLİŞSEL FONKSİYONLARININ DEĞERLENDİRİLMESİ

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Anahtar Sözcükler: çocukluk çağı, epilepsi, bilişsel fonksiyonlar, karbamazepin

ABSTRACT

The aim ofthis study is to investigate the cognitive functions ofpatients who received carbamazepine and to determine the effect of carbamazepine on seizure control and thyroid functions.

The study was performed on 30 children with primary idiopathic epilepsy. The cognitive functions of the patients were evaluated according to Wechsler Intelligence Scale for Children-Revised.

*While total IQ scores of the patients remained in normal ranges during the study periode, çuotients for arithmetic and picture arrangement subtests were found to be significantly decreased by the 12*h month when compared with pretreatment and 6? month scores and çuotients for object assembly subtest by the* 6* *and 12® months when compared with the pretreatment score. The treatment led considerable decrease in serum T4, FT4 and FT3 levels at the* ö"1 *and 1Z?h months when compared with the pretreatment values. There was a significant correlation between the decrease in serum FT4 level at the* ö"7 *month and object assembly and also between the decrease in serum FT3 level at 12 month and decode subtest quotients.*

Our results suggest that epileptic children receiving carbamazepine have to be examined with WISC-R subtests during the follow-up to support the deficient subjects.

ÖZET

Bu çalışmanın amacı karbamazepin alan hastalarda bilişsel fonksiyonların araştırılması ve karbamazepinin nöbet kontrolü ve tiroid fonksiyonları üzerine olan etkilerinin saptanmasıdır

Çalışma primer idyopatik epilepsili 30 hasta üzerinde gerçekleştirilmiştir. Hastaların bilişsel fonksiyonları Wechsler Çocuk Zeka Ölçeği (WISC-R) ile değerlendirilmiştir.

Çalışma süresi boyunca hastaların total IQ skorları normal sınırlar içinde kalırken aritmetik ve resim düzenleme alt testlerinin 12. aydaki puanlarının tedavi öncesi ve 6. aya göre ve parça birleştirme alt testinin 6. ve 12. aydaki puanlarının tedavi öncesine göre anlamlı olarak azaldığı saptanmıştır. Serum T4, serbest T4 ve serbest T3 değerlerinin tedavinin 6.

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ve 12. ayındaki değerlerinin tedavi öncesi değerlerine göre belirgin olarak azaldığı tesbit edilmiştir. Serum serbest T4 düzeyinde 6. ayda gözlenen azalma ile parça birleştirme alt test puanı arasında ve serum serbest T3 düzeyinde 12. ayda gözlenen azalma ile şifre çözme alt test puanı arasında negatif ilişki saptanmıştır.

Çalışmamızın sonuçlan karbamazepin alan epileptik çocuklara eksik oldukları alanları desteklemek amacıyla izlem sırasında WISC-R alt testlerinin uygulanmasının gerekliliğini düşündürmüştür.

INTRODUCTION

Problems of cognition, leaming and behavior are frequent in children with epilepsy. The factors that may contribute to this impairment include type, frequency and duration of the seizure, preexisting brain damage, interictal epileptic discharges and psychosocial factors (1). In last decades, however, attention has been shifted to the effects of antiepileptic drugs (AED). It is generally confirmed that cognitive functions are impaired at high serum levels of AED (2). Carbamazepine (CBZ) is stili one of the most prescribed anticonvulsant drugs, it is effective in the control of patients with partial and generalized seizures (3). In the present study, we aimed to investigate the cognitive functions of the patients who received CBZ and to point the effects of the agent on cognitive functions regarding seizure type and frequency, electroencephalogram (EEG) findings, serum levels and liver and thyroid functions.

PATIENTS AND METHODS

This study was performed in 30 children (19 female, 11 male) with primary idiopathic epilepsy diagnosed in Pediatric Neurology Department. The median age of the patients was 10.6±3.0(6-16). The patients were of those with no other systemic or central nervous system disease and developmental retardation and who had never received any AED. The neurologic examinations and neuroradiologic investigations including brain MRI of the patients were ali normal. Seizure types were classified according to the criteria of International League Against Epilepsy (ILAE) as partial, secondary generalized and primary generalized (4). The CBZ blood levels has been detected within therapeutic ranges during the study period. The Wechsler Intelligence Scale for Children-Revised (WISC-R) was administered at the beginning of the study and repeated by the 6th and 12* months after the antiepileptic agent had been prescripted. Full scale, verbal and performance IQ were determined. If the patient had experienced any seizure, the WISC-R procedure had been delayed for one week.

Pertinent effects on the cognitive functions of the cases were asseyed and observed by correlating, pretreatment, 6th and 12th month EEG results after classifying as normal, epileptically focused (right or left) and multifocally discharged as well as regarding the type and frequency of seizures and regulations in the CBZ dose within the same intervals.

Thyroid hormones levels by the 6th and 12th months of the treatment were compared with those of pretreatment and changes were suspended for the effects on cognitive functions. CBZ involved treatment was scuritinized for not alone the effects it might cause but

well also for the efficiency on controlling the seizures and effect on liver enzymes. A few side effects of CBZ have been observed, but they did not allow to discontinue the treatment. ,

The results collected during the follow-up were precessed using a Statistical Package for the Special Sciences (SPSS). Statistical analysis was done using the repeated variance analysis for the changes of ali data in 3 different time interval and $p<0.05$ was accepted as significant. Paired-t test was done for detection in which time interval the established significant value is present. The relationship between seizure type and

WISC-R scores were statistically evaluated by using Mann-Whitney U test. A p value of less than 0.05 was statistically significant. The relationship between cognitive functions and seizure type, seizure frequency and EEG findings were evaluated by using Pearson correlation analysis.

RESULTS

CBZ proved a certain control on the seizures of 20 (66.6%) of the cases by the 6th and 26 (86.6%) by the 12th month of the treatment. CBZ blood levels were ali determined between 4-12 mg/dL. It has been established that changes in serum levels of CBZ did not influence the cognitive functions, as long as they were in therapeutic ranges. While ali others stayed unchanged, the only protrudion among the liver enzymes was of gamma glutamyl transferase (GGT) enzymes, significantly increased by the 6th month, further registered invariable by the 12th month.

Cognitive functions, when scaled by WISC-R, monitored quotients for arithmetic subtest, receded significantly by the 12th month when compared with pretreatment and 6* month scores along with the quotients for picture

arrangement subtest by the 12* month when compared with 6th month and finally quotients for object assembly subtest by the 6th and 12th months when compared with the ones applied pretreatmently (Table 1). Nevertheless, total IQ scores of the patients have been found between the normal ranges. There was no correlation between the cognitive functions and the type of the seizures when they happened to partial and/or secondary generalized or primarily tonic-clonic generalized (Table 2). A negative correlation has been detected between the multifocally EEG and similarities subtest (Table 3). Also a negative correlation has been detected between the frequency of seizures by the 6* month and the block design subtest (Table 4). Of the thyroid hormones, although they remained in normal range, serum thyroxine (T4), free thyroxine (FT4) and free triiodothyronine (FT3) are the ones that the treatment led significant changes versus serum triiodothyronine (T3) and thyroid stimulating hormone (TSH) levels indicated unchanged. While serum T4, FT4 and FT3 levels at the 6th and 12th months were decreased considerably when compared with pretreatment values, so did the serum FT4 level of the 12th month when compared with the 6th month's (Table 5). There was a significant correlation between the decrease in serum FT4 level at 6* month and object assembly subtests quotients and also between the decrease in serum FT3 level at 12th month and decode subtests guotients (Table 6).

Table 1. WISC-R scores of the patients at the 0th, 6th and 12th months of the treatment

WISC-R	before treatment	6th month	12th month	P
Verbal tests				
General knowledge	8.17±3.95	8.27±3.65	8.43±3.87	0.802
Similarities	8.60±5.16	8.20±4.16	8.60±3.85	0.723
Arithmetic	10.50±4.25	10.30±4.36	9.23±3.80	0.001*
Judgement	7.13±3.07	7.0±3.06	6.53±3.36	0.301
Vocabulary	7.60±3.12	7.80±3.07	4.07±3.50	0.298
Performance				
Picture completion	8.90±3.55	9.27±3.34	9.67±3.68	0.242
Picture arrangement	9.33±4.58	8.53±3.80	9.63±4.36	0.022
Design with cubes	10.00±3.01	10.17±2.98	10.57±3.51	0.351
Object assembly	8.77±3.69	10.23±3.24	10.57±4.04	0.001*
Decode	13.53±4.57	13.30±4.56	17.43±5.68	0.300
Verbal score	89.77±22.22	89.20±19.75	90.23±19.51	0.789
Performance score	91.50±25.81	95.87±19.41	99.87±21.21	0.068
Total score	92.63±21.22	93.17±18.91	93.90±18.82	0.699

Table 2. The comparison of the pretreatment WISC-R scores of the patients in regard to seizure types

WISC-R	Partial, Secondary generalized seizure (n:16)	Generalized tonic-clonic seizure (n:14)	P
General knowledge	8.50±4.53	7.79 2.37	NS
Similarities	8.56±5.55	8.64±4.85	NS
Arithmetic	10.44±4.05	10.57±4.31	NS
Judgement	6.94±3.57	7.36±2.37	NS
Vocabulary	7.13±3.90	8.14±1.92	NS
Picture completion	8.88±4.53	9.71±3.15	NS
Picture arrangement	8.25±4.67	10.57±4.31	NS
Design with cubes	9.94±3.11	10.07±3.00	NS
Object assembly	7.56±3.76	10.14±3.21	NS
Decode	15.56±6.49	10.86±3.46	NS
Verbal score	89.75±23.92	90.64±17.52	NS
Performancescore	84.06±23.92	100.35±15.82	NS
Total score	89.56±23.94	96.14±17.85	NS

NS: non significant

Table 3. The comparison of the pretreatment WISC-R scores of the patients in regard to EEG findings

WISC-R	Focal (right) (n:10)	Focal (left) (n:4)	Multifocal (n:10)	P
General knowledge	9.2±4.08	8±4.83	7.1±2.77	NS
Similarities	11.6±3.03	8.20±3.23	5.4±5.25*	p<0.05
Arithmetic	12.0±4.19	12.25±3.59	8.74±.22	NS
Judgement	6.9±2.69	6.24±2.22	7.9±3.21	NS
Vocabulary	8.3±2.63	81.0±.15	6.2±3.36	NS
Picture completion	8.4±4.06	9.75±1.26	8.6±3.1	NS
Picture arrangement	10.9±3.18	7.5±2.38	9.1±5.74	NS
Design with cubes	10.6±1.65	9.75±2.06	10.6±3.84	NS
Object assembly	9.8±3.88	10.25±1.83	8.0±3.86	NS
Decode	12.3±3.32	10±1.83	11.4±4.3	NS
Verbal score	98.6±18.58	91 ±22.72	81.2±19.88	NS
Performance score	99.5±19.09	95.5±4.93	84.2±34.29	NS
Total score	99.7±18.54	93.0±13.83	88.2±22.55	NS

NS: non significant

Table 4. The correlation between WISC-R scores and number of seizures before treatment, between the first and second test and between the second and third test

WISC-R	n* before 1. test		n between 1. and II. test		n between II. and III. test	
	r	P	r	P	r	P
Verbal tests						
General knowledge	0.1215	0.522	0.1659	0.381	0.1328	0.484
Similarities	0.0108	0.955	0.072	0.724	0.1730	0.361
Arithmetic	0.125	0.511	0.1496	0.430	0.933	0.624
Judgement	0.975	0.608	0.977	0.608	0.106	0.956
Vocabulary	-0.1722	0.363	0.1099	0.387	0.2037	0.280
Performance						
Picture completion	-0.1502	0.428	0.985	0.310	0.625	0.345
Picture arrangement	- 0.0301	0.874	0.1302	0.453	0.3257	0.079
Design with cubes	0.1227	0.518	- 0.4903**	0.006**	0.2705	0.148
Object assembly	-0.1011	0.595	0.2541	0.497	0.1290	0.497
Decode	0.476	0.803	0.985	0.605	0.625	0.743
Verbal score	0.334	0.861	0.1637	0.387	0.1950	0.302
Performance score	- 0.2252	0.231	0.2465	0.819	0.1238	0.514
Total score	-0.252	0.894	0.2522	0.179	0.1881	0.319

* Number of seizures ** Pearson correlation analysis, p<0.05

Table 5. The mean values of the thyroid hormones at the 0th, 6th and 12th months of the treatment

Thyroid hormones	before treatment	6th month	12* month	P
T4 (ug/dL)	8.23±1.78	7.14±1.18	6.80±1.55	0.001*
T3 (ng/mL)	1.69±0.68	1.47±0.35	1.52±0.43	0.153
TSH (nlU/mL)	2.45±1.48	2.79±1.36	2.81±1.19	0.302
FT4 (ng/dL)	1.35±0.4	1.17±0.3	0.95±0.2	0.004*
FT3 (pg/mL)	3.49±0.44	3.21±0.45	2.96±0.65	0.001*

Table 6. The correlation between WISC-R scores and T4 values at the 0th, 6th and 12lh months of the treatment

WISC-R	T4 values before treatment		T4 values at the 6th month		T4 values at the 12* month	
	r	P	r	P	r	P
Verbal tests						
General knowledge	-0.1673	0.377	0.2070	0.272	0.0431	0.821
Similarities	- 0.2659	0.156	-0.1729	0.361	0.369	0.035*
Arithmetic	- 0.2026	0.273	0.1515	0.424	0.1432	0.450
Judgement	-0.512	0.788	0.3676	0.036*	0.3261	0.038*
Vocabulary	- 0.635	0.739	0.2910	0.036*	0.3843	0.739
Performance						
Picture completion	-0.3125	0.93	0.1644	0.389	0.3148	0.09
Picture arrangement	-0.1876	0.321	0.4202	0.021*	0.4578	0.011*
Design with cubes	- 0.2771	0.138	- 0.284	0.881	- 0.208	0.913
Object assembly	- 0.3481	0.59	-0.1301	0.493	0.1009	0.596
Decode	0.417	0.939	0.556	0.771	0.0556	0.219
Verbal score	-0.2151	0.253	0.1873	0.322	0.1741	0.358
Performance score	-0.1885	0.319	0.0383	0.84	0.1220	0.521
Total score	- 0.2995	0.108	0.1818	0.336	0.1056	0.578

* Pearson correlation analysis, $p<0.05$

DISCUSSION

The quality of life has become an important issue in epileptic patients as well as in ali chronic diseases for the past years. The objective of the treatment is not only to control the seizures, but also to dissolve the cognitive, behavioral, psychological and educational problems (5). A special type of behavioral or cognitive dysfunction has not been defined in epileptic patients. İt has been well known that cognitive dysfunction, learning disabilities and behavioral problems can occur regardless of treatment. Even though it has not been clear that AED have a negative effect on cognitive functions, it has been shown that those drugs play a negative role in this dysfunction (6).

CBZ is a majör AED which has been used particularly in partial and generalized tonic-clonic seizures for many years. In our study, with the CBZ treatment, seizures have been controlled in the 6th month 66.6% of our cases and in 12th month 86.6% of our cases. İn recent studies it has been reported that successful seizure control has a positive effect on cognitive function (7,8).

There are also studies which reported no negative effect of CBZ on cognitive functions in therapeutic ranges of serum levels (6). In our study, it was detected that CBZ medication do not affect the cognitive functions as long as serum levels have been detected in therapeutic ranges. This fact is also in agreement with literatüre findings (6,9).

By patients who received CBZ therapy approximate quotient of the WISC-R arithmetic subgroup was found significantly decreased in the 12* month of treatment compared to prior to treatment and to the 6th month of the treatment period. The approximate quotient of the object assembly subtest results was found significantly decreased in the 12th and 6th month of the treatment compared to pretreatment values. İn the picture arrangement subtest, the approximate quotient was significantly decreased only in the 12th month compared to the 6th month. The results of other studies on the effect of CBZ treatment on the cognitive functions are showing differences (10,11). A recent study in epileptic children showed that CBZ caused a decrease in the arithmetic and picture arrangement subtests (12). There are studies reported no negative effect of CBZ on cognitive functions (6).

In our study, type of seizure, EEG abnormality, localization on EEG and frequency of seizure were evaluated as relating factors on cognitive functions. There was no correlation found between the type of seizure and cognitive functions. İt has been reported that there is a correlation between the type of seizure and cognitive functions (13). IQ scores were found less in

patients with generalized seizures than in patients with seizures, memory was affected more and cognitive performance was decreased (14). There have also been studies reporting that IQ scores were better in patients with partial seizures receiving CBZ (5,15). We cannot make any interpretation in this subject because of the inadequate number of patients in our study.

We found a negative correlation between similarities subtest and multifocally EEG findings. Even though in the literatüre there are some studies reporting that patients with right focused and multifocally EEG showed more negative prognosis than the patients with left focused EEG finding, there are also some studies which have opposite results (7). İt has been reported that in the left focused EEG group, there is learning disability, speech disturbance and serious problems in recognizing the number series and that in the right focused group there is visual function disability, deficiency in numerical comprehension and attention deficit (16,17).

When the correlation between the seizure frequency and cognitive functions is examined, there was a negative correlation found between the seizure frequency which was undergone prior to the second test and block design subtest. İt was also reported that long duration of epilepsy, frequent seizure attacks or combination of these two might cause cognitive dysfunction (18).

The serum levels of T3, T4, FT3, FT4 and TSH were found normal before the treatment. İn the 6^{th} month of treatment, there was found a significant decrease when serum T4, FT4, FT3 levels were compared with the pretreatment levels even though between the normal ranges. Identically, in the 12^{th} month of treatment, the serum levels of T4 and FT3 were found significantly decreased when compared with the pretreatment values. Previous studies reported that CBZ decreases the serum levels by accelerating the metabolism of thyroid hormones and, level of serum TSH remains stable (19-20). In our study, we might condude that the level of T3 did not decrease because T3-T4 cycle was not disturbed and also, the serum level of TSH did not decrease because T3 level was normal or patients with partial seizures. Also in patients with generalized normal functioning hypophisis and thyroid axis might compensate this situation (21).

In this sudy, WISC-R subtests and thyroid hormone correlation was investigated considering the possibility that CBZ might have an effect on cognitive functions by affecting thyroid hormones and a positive correlation has been found between the levels of T4, FT4, FT3 and some WISC-R subtests. İn two different previous studies, it has been reported that CBZ can cause a decrease in thyroid hormone levels but that has no effect on cognitive functions (22,23). Refering some subtests, the changes of thyroid hormones levels believed to have been induced by the agent as a side effect, might very well be suggested to have deteriorate the cognitive functions. Afterall we suggested that the reducing in serum T4 level at the 6* month of treatment caused decrease in picture arrangement, vocabulary and comprehension subtests quotients. Similarities and picture arrangement subtests were also reduced due to the decrease by the 12^{th} month interval. Our results support that çare should be taken for the patients who receive CBZ treatment because of the possibility of decrease in T4, FT4, FT3 levels. Nevertheless, more detailed studies are needed to make any interpretations.

Our study showed that, only GGT levels among liver function tests were increased significantly during treatment. CBZ initiates synthesis of GGT which is a microsomal enzyme and, therefore may be the reason for the increased serum values in 25-90% of epileptic patients (2). A significant increase in GGT levels in the 6^{th} month was detected and this high value persisted in the 12* month without any continuation of the increase. That result might indicate that CBZ produces microsomal enzyme induction during early periods of treatment.

İn conclusion, our results suggest that, epileptic children receiving CBZ have to be examined with WISC-R subtests during the follow-up period to support the deficient subjects.

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