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Assessment of vestibulo-ocular reflex with video head impulse test in epilepsy patients undergoing carbamazepine monotherapy

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Abstract. – OBJECTIVE: Carbamazepine may cause clinical effects such as dizziness and nystagmus. This may depend on the duration of use. The aim of this study is to measure the effect of carbamazepine monotherapy on the vestibular system electrophysiologically by using Video Head Impulse Test (VHIT) and to compare the numerical and objective data obtained between the groups.

PATIENTS AND METHODS: In this study, in which 55 people (110 ears) participated, Video Head Impulse Test (VHIT) was performed to evaluate the vestibulo-ocular reflex (VOR) in the epilepsy patients and a healthy control group consisting of healthy individuals. In addition, patients were analyzed in two groups to demonstrate the long-term effects of carbamazepine (<10 years and >10 years). Right/left lateral, anterior, posterior semi-circular canals (SCCs) VOR gains, lateral, left anterior right posterior, and right anterior right posterior gain asymmetries were measured between groups.

RESULTS: Lateral SCCs VOR gains were 0.878±0.057 and 0.921±0.045 between the patient and healthy control groups, respectively (p=0.024). A decrease in the right and left lateral SCCs VOR gains (0.885±0.062 and 0.868±0.063) was detected in the patients (p=0.011 and p=0.001). Those using carbamazepine for >10 years had a decrease in lateral SSCs VOR gains (0.843±0.055) compared to those using the drug for <10 years (0.902±0.046) (p=0.008).

CONCLUSIONS: A relative reduction in lateral (right/left) SCCs VOR gains was found in epilepsy patients using carbamazepine and in the group of patients using this drug for a long time (>10 years).

Key Words:
Carbamazepine, Epilepsy, Video head impulse test, Vestibular system, Vestibulo-ocular reflex.

Introduction

Carbamazepine is used for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. It is known that approximately one-third of epilepsy patients use antiepileptic drugs (AEDs) for life[1]. Carbamazepine has been used in Europe since 1965, especially in focal-onset seizures and generalized tonic-clonic seizures[2,3]. The bioavailability of orally taken carbamazepine is 75-85%. Almost all of the drug is metabolized by epoxidation and hydroxylation reactions in the liver, and its plasma protein binding rate reaches 70-80%[4]. Mild and transient skin reactions are a common finding when starting the drug in patients using carbamazepine. However, cases[5,6] reporting some early or long-term subclinical effects related to the drug have been published. Dizziness, ataxia, nystagmus, depressed optokinetic nystagmus, and saccadic-smooth eye movement tracking disorders have all been reported in long-term phenytoin and carbamazepine users.

Vestibular System and Vestibulo-Ocular Reflex

The vestibular system is a sensory system that enables movement to take place in harmony and includes postural muscles, the ocular system, and structures such as the brainstem, cerebellum, and cortex. While the peripheral vestibular system includes the semi-circular canals (SCCs), utricle, saccule, vestibular nerve, and vestibular ganglion, the central vestibular system includes the vestibular nuclei, secondary neurons, and their central connections[7,8]. In this study, vestibulo-ocular reflex (VOR) was evaluated by the Video Head Impulse Test (VHIT). VHIT is used to obtain the VOR gain and asymmetry data of the SCC. There are three SSCs that detect angular movements of the head: posterior (inferior), anterior (superior), and lateral (horizontal). Each SCC is sensitive to movement in a certain plane. However, SCCs on one side are not sufficient to detect angular movements. In the contralateral ear, each SCC has a symmetrical canal. Angular motion is perceived

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by the formation of different electrical potentials in the symmetrical SCCs as a result of the angular movement of the head[9]. The VOR fixes the objects in the visual field in the fovea of the eye during head movements, allowing us to see still and clearly. It does this by moving the eye at an equal speed in the opposite direction of the head movement[10]. The VHIT is a tool for the assessment of the VOR. This test objectively measures the ratios of head and eye speeds and SCCs gains[11]. The primary use of VHIT is to detect peripheral vestibular dysfunction and distinguish between peripheral and central vestibular disorders[12].

Epilepsy patients usually take long-term drug therapy. While some drugs may cause clinically apparent adverse effects even in the first days of treatment, such an adverse reaction is not observed in many others. In this study, it was aimed to show the effect of carbamazepine on the peripheral vestibular system. Although it was observed that the participants did not have symptoms such as active vertigo and dizziness, the presence of pathology affecting the subclinical vestibular system was investigated through VHIT. Our hypothesis was that carbamazepine affects VOR in the patient group due to the long-term use of the drug.

Patients and Methods

This research was planned as a prospective, case-control study and was conducted in the Neurology and Otolaryngology Departments of a university hospital in Eastern Turkey.

The patients and healthy volunteers who participated in the study were informed about the study and signed an informed consent form. During the study, the approval of the University's Ethics Committee was obtained before the research, and the study was conducted by paying attention to the criteria in the Declaration of Helsinki (Ethics App. 4429).

Study Population and Data Collection

A total of 55 people participated in the study. The participants were divided into two groups as the patient and healthy control group. Individuals with a definite diagnosis of epilepsy in the Neurology Department formed the patient group with the following inclusion criteria: taking carbamazepine monotherapy, coming for at least 2 follow-ups in the last 1 year, being compatible for VHIT, and good cognitive cognition, exclusion criteria; patients who do not use carbamazepine regularly, use drugs other than AEDs due to chronic disease, the duration of carbamazepine use is uncertain, and already have active vestibular symptoms or signs (vertigo, nystagmus, dizziness, etc.).

VHIT was performed by a specialist audiologist for both groups, and the results were recorded simultaneously, and those whose hearing test was not normal for the patient and control groups were excluded from the study.

After the test, the results were reviewed by an otolaryngologist. For epileptic patients, the daily dosage and duration of use of carbamazepine (mg/day), and electroencephalography (EEG) information were checked over the electronic files. EEGs were taken in our center, and EEG recordings were analyzed by a neurologist. To control the proper use of the drug by the patients, the blood drug level of carbamazepine was measured in the laboratory by drawing blood from the peripheral venous route.

Video Head Impulse Test

Micromedical Technologies® (EyeSeeCam model, Munich, Germany) VHIT device was used in this study. While the patient was sitting upright, glasses were put on, and he was asked to look at the target from one meter away. Head and eyes were calibrated. The patient's head was moved with small amplitude and high speed in the direction of the lateral SCCs, the right anterior left posterior SCCs, and finally, the left anterior right posterior SCCs while the patient was looking at the target. While eye movements were recorded with the camera on the glasses, the gain value was determined by calculating the head speed with the help of the sensor. As a result of the test, gain, presence of saccade, and percentage of asymmetry were evaluated. The asymmetry value was calculated, and the SCCs that were symmetrical to each other were compared. Gain refers to the ratio of head and eye speed to each other. In normal individuals, this ratio is 1. In the presence of pathology affecting the VOR reflex, this rate decreases, and it is considered significant if it is lower than 0.7[13]. Gain asymmetry was calculated according to the Jongkees formula (Gain asymmetry=100 x (Left-side gain – Right-side gain)/(Left-side gain + Right-side gain)[14].

Statistical Analysis

SPSS® 26.0 (IBM Corp., Armonk, NY, USA) package program was used for statistical analysis. The conformity of the data to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Skewness

and Kurtosis tests). In summarizing numerical data, arithmetic mean, standard deviation, minimum and maximum values, frequency distributions, and percentages were used to summarize categorical data. The Independent Samples *t*-test was used to compare the VHIT results of the two groups regarding independent variables, patient-control groups, and carbamazepine duration. The Chi-square test was used for independent categorical variables (group, gender, etc.). $p<0.05$ was considered significant in all statistical interpretations.

Results

A total of 55 individuals (110 ears), 25 patients, and 30 controls were included in the study. Gender distribution in the patient and control groups were, respectively, 17 (68%) and 20 (66.7%) males, 8 (32%), and 10 (33.3%) females ($p=1.001$). The mean age was 32.4±10.8/year in the patients and 37.8±11.5/year in the healthy control group ($p=0.079$). Detailed clinical and demographic data of epilepsy patients are presented in Table I.

First, the VHIT results were compared between the two groups. Lateral SCCs VOR gains of the patient and control groups were detected as 0.878±0.057 and 0.921±0.045, respectively ($p=0.024$). Then, right and left lateral SCCs VOR gains between both ears were examined in both groups. Right/left lateral SCCs VOR gain was 0.885±0.062/0.868±0.063 in patients, while it was 0.911±0.058/0.926±0.049 in controls ($p=0.011$/$p=0.001$). Also, right and left lateral SCCs VOR gains between both ears were examined in both groups. While the right/left lateral SCCs VOR gain in patients was 0.911±0.058/0.926±0.049 in controls ($p=0.011$/$p=0.001$).

Right anterior left posterior (RALP) asymmetry gains were measured as 3.076±2.827 and 1.453±1.436 in the patient and control groups, respectively ($p=0.014$). Detailed VHIT results between both groups are shown in Table II.

Epilepsy patients were divided into two groups according to the duration of carbamazepine use. 60% (n: 15) of the patients were using carbamazepine for 10 years or less. The effect of the duration of the use of carbamazepine monotherapy (<10 years and >10 years) on VHIT outcomes was investigated. When all parameters were compared, it was seen that there was a difference between the individual lateral SSC VOR gains.

Carbamazepine usage for <10 years and >10 years and lateral SCC VOR gains was measured as 0.902±0.046 and 0.843±0.055, respectively ($p=0.008$). When we look at both ears as

Table I. Demographic and clinical characteristics of participants individuals.

Age		
• Patients	32.4±10.8	$p=0.079$
• Controls	37.8±11.5	
Gender		
• Patients n (%) m/f	17 (68%)/8 (32%)	$p=1.001$
• Controls n (%) m/f	20 (66.7%)/10 (33.3%)	
CBZ monotherapy duration, n (%)		
• ≤10 years	15 (60%)	
• >10 years	10 (40%)	
Characteristics of epilepsy patients, mean (min-max)		
• Age of diagnosis	21.48±11.55 (3-44)	
• Disease duration	11.04±7.25 (2-31)	
• Seizure/year	3.48±1.44 (1-6)	
• CBZ mg/day	928.1±222.7 (400-1600)	
Types of seizure, n (%)		
• GTCS	7 (28%)	
• CPS	11 (44%)	
• Focal seizure	4 (16%)	
• Unknown seizure types	3 (12%)	
Types of EEG, n (%)		
• Generalized epileptic	8 (32%)	
• Left hemisphere epileptic	10 (40%)	
• Right hemisphere epileptic	4 (16%)	
• Multifocal epileptic	3 (12%)	

m: male; f: female; CBZ: carbamazepine; GTSC: generalized tonic-clonic seizure; CPS: Complex partial seizures; EEG: electroencephalogram.

Table II. Comparison of VHIT results between epilepsy patients and healthy controls.

	Patiens		Controls			95% Confidence Interval of the difference		
	Mean	Std. Deviation	Mean	Std. Deviation	*t*	Lower	Upper	*p*
Right Lateral SCC VOR Gain	0.885	0.062	0.911	0.058	-1.619	-0.0592	0.0063	0.011
Left Lateral SCC VOR Gain	0.868	0.063	0.926	0.049	-3.821	-0.0884	-0.0275	0.001
Lateral SCCs VOR Gain	0.878	0.057	0.921	0.045	-3.052	-0.0704	-0.0145	0.004
Lateral Gain Asymmetry	2.476	1.813	2.713	1.650	-0.503	-1.1749	0.7002	0.614
Left Anterior SCC VOR Gain	0.886	0.072	0.874	0.068	0.593	-0.0270	0.0496	0.556
Right Anterior SCC VOR Gain	0.860	0.068	0.883	0.051	-1.429	-0.0552	0.0092	0.159
Anterior SCCs VOR Gain	0.875	0.050	0.881	0.048	-0.427	-0.0326	0.0211	0.671
Right Posterior SCC VOR Gain	0.887	0.077	0.885	0.069	0.131	-0.0371	0.0423	0.896
Left Posterior SCC VOR Gain	0.838	0.092	0.878	0.059	-1.921	-0.0809	0.0017	0.072
Posterior SCCs VOR Gain	0.866	0.075	0.884	0.051	1.092	-0.0529	0.0156	0.280
LARP Gain Asymmetry	2.524	2.258	2.243	1.896	0.501	-0.8429	1.4043	0.618
RALP Gain Asymmetry	3.076	2.827	1.453	1.436	2.603	0.4390	2.8062	0.014

SSC: semicircular canal; VOR: Vestibulo-ocular reflex; LARP: left anterior right posterior; RALP: right anterior left posterior.

right and left alone, in those using carbamazepine for 10 years or less, the right/left lateral SSC VOR gain was 0.910±0.041/0.890±0.060, while the right/left lateral SSC VOR gain was 0.847±0.071/0.834±0.053 in those who used the drug for more than 10 years (p=0.010/p=0.024).

Detailed information on the VHIT results of long-term use of carbamazepine is presented in Table III.

Discussion

Epilepsy is one of the most common neurological diseases. The prevalence of epilepsy in the general population is estimated to be 8.2-12.9/1,0001. Considering that epilepsy patients have been using AEDs for many years, some adverse reactions may be seen in the acute or chronic period due to these drugs. In the literature, the effect of carbamazepine on the auditory and vestibular system has been reported. However, when these publications on the vestibular system are examined, it is seen that they were based on symptoms and clinical findings, and there was no study in the literature that evaluates the relationship between carbamazepine and VOR with objective and numerical results. In case reports where the VIII cranial nerve is affected due to antiepileptic agents, we mostly come across publications on hearing loss. There are few case reports1[5,16] of reversible or irreversible hearing loss with the use of valproate and carbamazepine. In a study[17], it was reported that carbamazepine and oxcarbazepine had

Table III. Comparative analysis of VHIT results between patients with carbamazepine monotherapy 10 years-period.

	≤10 years		>10 years			95% Confidence Interval of the difference		
	Mean	Std. Deviation	Mean	Std. Deviation	*t*	Lower	Upper	*p*
Right Lateral SCC VOR Gain	0.910	0.041	0.847	0.071	2.817	0.0169	0.1104	0.010
Left Lateral SCC VOR Gain	0.890	0.060	0.834	0.053	2.409	0.0080	0.1053	0.024
Lateral SCCs VOR Gain	0.902	0.046	0.843	0.055	2.918	0.0173	0.1019	0.008
Lateral Gain Asymmetry	2.420	1.296	2.560	2.477	-0.185	-1.7032	1.4232	0.855
Left Anterior SCC VOR Gain	0.890	0.082	0.880	0.058	0.330	-0.0526	0.0726	0.744
Right Anterior SCC VOR Gain	0.868	0.064	0.847	0.074	0.772	-0.0363	0.0796	0.448
Anterior SCCs VOR Gain	0.881	0.059	0.867	0.035	0.682	-0.0291	0.0578	0.502
Right Posterior SCC VOR Gain	0.908	0.085	0.856	0.053	1.727	-0.0104	0.1157	0.098
Left Posterior SCC VOR Gain	0.839	0.090	0.837	0.101	0.061	-0.0773	0.0820	0.952
Posterior SCCs VOR Gain	0.876	0.080	0.850	0.067	0.865	-0.0371	0.0904	0.396
LARP Gain Asymmetry	2.620	2.028	2.380	2.676	0.255	-1.7060	2.1860	0.801
RALP Gain Asymmetry	3.180	2.315	2.920	3.596	0.221	-2.1766	2.6966	0.827

SSC: semicircular canal; VOR: Vestibulo-ocular reflex; LARP: left anterior right posterior; RALP: right anterior left posterior.

a decreasing effect on musical pitch perception. Brainstem auditory evoked potentials have been evaluated in electrophysiological studies1 on the effects of antiepileptic drugs on the central system, but different results have been reported by the authors. There are publications[5] stating that individuals using carbamazepine have negative signs and symptoms due to the involvement of the vestibular system. Hamed et al[5] reported frequent vestibular symptoms, including dizziness (62%) and a sense of unsteadiness (44%) in patients with epilepsy treated with carbamazepine in the interictal period. In the same study, the authors emphasized that 24% of patients with epilepsy had central vestibular dysfunction, and 20% had mixed center and peripheral vestibular dysfunction. The vestibular signs detected were abnormal saccadic (44%) and follow-up (42%), eye movements, optokinetic nystagmus (42%), position/position (11%), and calorie testing (13%). In this study, the authors concluded that chronic epilepsy and long-term treatment with carbamazepine resulted in negative vestibular symptoms.

When we compare the VHIT results between the patient and control groups in our study, we see that there are no abnormal results in general. However, there was a difference in the right and left lateral SSC VOR gains between the two groups. Right and left lateral SSC VOR gains in the epilepsy group were 0.885±0.062 and 0.868±0.063 ($p<0.05$). In the control group, we saw that these results were higher, closer to +1. Since the lateral SSC VOR gains in the patient group did not fall below 0.7 for both ears, it cannot be interpreted as an abnormal result. Based on the data obtained in this study, we can say that carbamazepine caused a relative decrease in lateral SCC VOR gains. Lateral VOR asymmetry, left anterior right posterior (LARP), and RALP results were similar between the two groups.

Mervaala et al18 reported that carbamazepine prolongs the latency of cortical somatosensory evoked potentials (SSEP), while valproic acid did not cause SSEP abnormalities. Zgorzalewicz[19] found prolonged P100/N145 latencies and decreased N75/P100, P100/N145 amplitudes in Visual evoked potentials (VEP) records in chronic users of carbamazepine. In another electrophysiological study[5] examining the effect of long-term use of carbamazepine on the vestibular system, it was observed that there was a prolongation of VEP P100 latency, a delay between SSEP N9-N20, and slowdowns in conduction at different levels. In this study[5], it was noted that there was a positive correlation between the dose of carbamazepine and the prolongation of P100 latency. Subclinical auditory and vestibular dysfunctions of carbamazepine are not uncommon, suggesting that long-term treatment will increase the progressive and permanent negative effect. Some authors1 emphasized that the risk of ototoxicity/vestibular toxicity is directly proportional to the dose. They even argued that these risks increase with the use of more than one AEDs.

In this study, we aimed to show the possible time-dependent vestibular effect of carbamazepine monotherapy in epilepsy patients. Therefore, we analyzed the VHIT results of patients using carbamazepine for 10 years or longer. Right and left lateral SCC VOR gains were found to be 0.847±0.071 and 0.834±0.053 in those who used the drug for more than 10 years, and there was a decrease in VOR gains compared to those who used the drug for 10 years or less ($p<0.05$). When we examined the lateral SCCs VOR gains in individuals using carbamazepine for more than 10 years ($p>0.05$), it was seen that long-term use of the drug negatively affects the VOR gain. Although this data is insufficient to say abnormal, it can be said that it causes a relative decrease in the lateral SSCs VOR gain. When the left/anterior-posterior and right/anterior-posterior VOR SCC gains of long-term use of carbamazepine over 10-year periods were analyzed between the two groups, it was observed that there was no significant difference.

Limitations

This study, which evaluates the effect of carbamazepine on the vestibular system with VHIT for the first time in the literature, has some limitations and deficiencies that can be completed in future studies. First of all, VHIT was not evaluated before starting the drug in epilepsy patients. The presence or absence of symptoms such as vertigo and dizziness, which may occur in the first days of carbamazepine-induced medication in the patient group, was not mentioned because the records were insufficient.

Conclusions

When we look at the effect of carbamazepine on the vestibular system through VHIT in the epileptic patient/control and short/long-term drug usage (<10 years and >10 years) groups: it has been determined that there is a difference in lateral (right/left) SCCs VOR gains. A relative reduction in lateral SCC VOR gains was analyzed in the patient group and the long-term (>10 years) drug user group. In this respect, it may be recommended to perform an audiological examination at the beginning of the drug

at certain periods, especially for patients who have used carbamazepine for a long time.

Conflict of Interest
The authors declare that there is no conflict of interest.

Ethics Approval
Ethics committee approval was obtained from Inonu University School of Medicine, Clinical Researches Ethics Committee (Number: 23/4429) and the principles of the Helsinki Declaration were followed.

Informed Consent
Written informed consent was obtained from the patients participating in the study, or their first-degree relatives if the patient was unable to provide consent, after informing them about the study rationale and their right to withdraw from the study at any time without any consequences.

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Authors' Contributions
ID: Planning, designing, data collection, literature survey. AA: Planning, designing, statistical analysis, interpretation of the results, writing, submission. All authors have agreed to the conditions noted on the Authorship Agreement Form. The authors read and approved the final manuscript.

Availability of Data and Materials
The complete de-identified dataset is available from the corresponding author on a reasonable request.

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