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The role of event related potentials in evaluation of subclinical cognitive dysfunction in epileptic patients

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Abstract

Background/ Aim : Cognitive dysfunction in epileptic patients may develop due to the neurophysiological changes related to seizures or antiepileptic drugs. The aim of this study was to evaluate the cognitive dysfunction in epileptic patients under antiepileptic drug therapy by the aid of event related potentials.

Method : P300 latencies were obtained from Fz, Cz and Pz electrod positions from both epileptic patients (n = 40) and age and sex matched control group (n = 40). Epileptic patients were classified either idiopathic primary generalized (IPGE) (n = 9) or secondary generalized epilepsy (SGE) (n = 31) based on the ILAE classification. The effect of epilepsy type, treatment types (monotherapy/ polytherapy), daily dosages and serum levels of antiepileptic drugs, age at onset and EEG abnormalities on P300 latencies were studied.

Results : P300 latencies were longer in the epileptics when compared to controls ($P < 0.05$). Besides, our results pointed out that P300 latencies were longer in IPGE when compared to SGE ($P < 0.05$). No statistically significant difference was determined between ERP parameters neither in monotherapy nor in polytherapy groups ($p > 0.05$). Antiepileptic drug subgroups revealed variable effects on ERP latencies.

Conclusion : We believe P300 latencies may have an important role in the evaluation of subclinical cognitive dysfunction in epileptic patients treated with antiepileptic drugs.

Introduction

Several groups of investigators have studied the cognitive changes in epilepsy, and results generally indicate that there is a decline of cognitive functions in epileptics especially in the memory, attention, concentration and speed of mental processing (1).

Event related potentials (ERP) and P300 record the electrical manifestations of brain's reception of and response to external stimulus (2). The P300 is the most commonly recorded event related potential (3). In general, the P300 latency is considered a measure of stimulus classification speed and reflects attention-related and memory processes (4). Because P300 peak latency increases systematically with the increase in cognitive dysfunction, it has been used as an objective electrophysiological index for the assessment of the degree of cognitive dysfunction (5), to study brain mechanism underlying cognition and to characterize information processing in normal and cognitively disabled population (6).

The aim of the present study was to evaluate auditory event related potentials (AERPs) from a group of epileptics in order to determine the possible correlation between neurophysiological data and certain characteristics of this population like seizure type, EEG findings, duration of disease, and the type of anticonvulsant treatment.

Material-method

The study involved 24 female and 16 male patients between the ages of 18 and 70 years (mean age : 36.5 ± 13.8 years). The patients with epilepsy were classified according to the revised criteria of International Classification of Epileptic Seizures (7). All the patients had 2 or more unprovoked seizures : either idiopathic primary generalized (IPGE) or secondary generalized seizures (SGE). Nine of the patients had idiopathic generalized seizures, while the remaining 31 patients had secondary generalized seizures according to the ILAE criteria. The duration of epilepsy ranged between 1 and 36 year(s) (mean : 11.39 years). The age at the onset of the seizures varied from 0 to 79 years (mean : 15.875 years).

All the patients were seizure free or satisfactorily controlled with antiepileptic drugs. Twenty-seven of the patients were receiving monotherapy, and 13 were receiving polytherapy. Eleven of those treated with polytherapy were receiving dual therapy, while two were receiving triple therapy (Table 1). Daily dosages of antiepileptic drugs have been provided in Table 2. Serum levels of valproic acid (VPA), carbemezapine (CBZ) and diphenilhidantoin (DPH) were within normal limits.

Table 1

Treatment types of epileptic patients

Drug name	Monotyherapy	Polytherapy	Total
VPA	16	6	22
CBZ	9	7	16
OXC	3	2	5
LMT	–	5	5
TPM	–	3	3
LVT	–	1	1
DPH	–	1	1

Table 2

Daily dosage of antiepileptic drugs

Treatment	Dose (per day)
VPA	250-1300 mg
CBZ	300-1200 mg
LMT	450-1800 mg
TPM	100-200 mg
DPH	300 mg
LVT	2500 mg

In the evaluation process, the patients with epileptic abnormalities and the patients with normal EEGs were determined. Then, the patients were divided into 3 groups according to their EEG abnormalities as : normal, diffuse background slowing and having epileptiform abnormalities. Eleven of the patients had normal EEGs, while 23 patients had epileptiform abnormalities, and the remaining 6 had diffuse background slowing. The magnetic resonance imaging (MRI) revealed hippocampal atrophy in 7 patients, while the MRIs of the remaining 33 patients were non-specific.

The history of the patients revealed no history of major head injury, congenital structural lesions, neurosurgical operations, alcohol or drug abuse, psychiatric illness and/or CNS disease other than epilepsy. None of the patients was on medication with the exception of anticonvulsants, and none had clinical signs of drug intoxication. Anticonvulsant drug serum levels of patients using VPA, CBZ or DPH were within normal values at the time of examination. None of the patients was examined within 48 hours of a seizure.

First, the patients were evaluated using Mini Mental State Examination (MMSE). Their scores were between 26 and 30 (mean : 29).

Recordings were performed using Nihon Kohden-Neuropack (MEB-5504 K) equipment. Evoked potentials were recorded from the scalp by colloidon mounted Ag/Ag Cl cup scalp electrodes (type : NE-132B) placed at CZ and PZ and were linked to the referred ears. Skin impedance was below 5 kΩ. The subjects were sitting comfortably with their eyes closed. They were instructed to mentally count the target tones but not the frequent tones and then asked to report the number of target tones counted at the end of each run. Rest periods were provided between test conditions as appropriate. ERP were elicited with an auditory discrimination task paradigm by presenting a series of binaural 1000 Hz (standard) versus 2000 Hz (target) tones at 70 dB with a 10ms rise/fall and 40 ms plateau times using DR-531-B10 ear phones. Tones were presented at a rate of 1.1 /s with target tones occurring randomly with a 0.2 probability. Filter settings were 0.1 and 50 Hz ; analysis time, 0.1 s ; sensitivity, 50 μv, and duration of stimulus, 0.1 ms. To assess the performance accuracy at the end of each session, each patient's count was compared with the actual number of target tones presented. Two or 3 trials were performed in order to demonstrate the consistency of the waveform (2).

Responses to target tone consisted of a prominent negative peak between 65 and 150 milliseconds, identified as N1, followed by a frontocentral positive wave (between 100 and 250 milliseconds) identified as P2. Responses to infrequent tone showed similar N1 and P2 followed by an additional through N2, and the paired, variably separated P300 peaks (8). P200 and P300 latencies were measured from the stimulus artifact to the first and second major positive peaks with a range 250 to 500 ms respectively (2). Amplitudes of event related potentials markedly varied normal controls. Thus, we mainly focused on the latency of ERPs and did not consider amplitudes of ERPs as a major index of an abnormality.

The control group consisted of 23 female and 17 male healthy subjects with a mean age of 38.9 ± 13.6 years. The controls and patients had comparable level of education and socioeconomic status. None of them was receiving any medication or had a history of a head injury, CNS disease, and alcohol or drug addiction. In addition, none had ever experienced a seizure.

Statistical analyses

The SPSS 12.0 package program was used to perform the statistical evaluation. The results were expressed as standard deviations from the mean. Non-parametric 'Mann-Whitney U' test was used to compare the means of two groups. To compare the means of three groups, Non-parametric 'Kruskall Wallis' test was used. Pearson's correlation of coefficiency was used when appropriate. $P < 0.05$ was considered significant.

Results

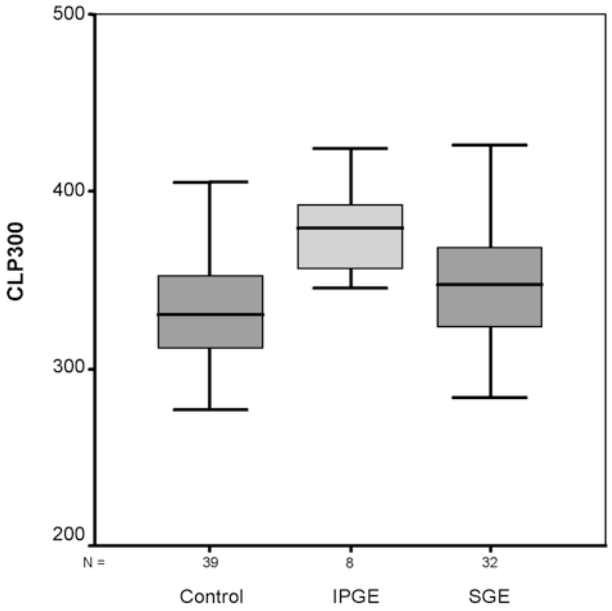
ERP results of the patients and controls have been presented in Table 3. There was a statistically significant prolongation of P300 latencies in epileptic patients compared to that of the controls ($p < 0.05$). Then, the data of epileptic patients were analyzed separately for those having SGE and for those having IPGE. The patients with SGE had N100

Table 3

The statistical analysis of ERP values in epileptic patients and in controls

Region	ERPs	Parameter	Group	Number	Mean	Range	P value
Frontal (Fz)	N100	Latency (ms)	Patient	40	100	80-164	0.233
			Control	40	95	68-129	
	N100	Amplitude (mV)	Patient	40	12.25	4.8-30	< 0.001*
			Control	40	7.3	2.6-13.6	
	P200	Latency (ms)	Patient	40	175	130-260	0.265
			Control	40	169	128-222	
	P200	Amplitude (mV)	Patient	40	9	3.3-38	< 0.001*
			Control	40	6	1.9-15.7	
	N200	Latency (ms)	Patient	40	238	176-350	0.573
			Control	40	231	195-309	
	N200	Amplitude (mV)	Patient	40	17.5	5-50	< 0.001*
			Control	40	9.4	3.1-26.3	
	P300	Latency (ms)	Patient	40	352	274-430	0.02*
			Control	40	316	244-369	
	P300	Amplitude (mV)	Patient	40	14.75	6.5-61.5	0.001*
			Control	40	10	3.1-26	
Central (Cz)	N100	Latency (ms)	Patient	40	98	80-160	0.341
			Control	40	95	68-124	
	N100	Amplitude (mV)	Patient	40	13.75	5.5-103	< 0.001*
			Control	40	9.3	2.8-17.6	
	P200	Latency (ms)	Patient	40	167	127-209	0.381
			Control	40	171	134-208	
	P200	Amplitude (mV)	Patient	40	9.75	4.5-29	< 0.001*
			Control	40	5.9	2.3-24.7	
	N200	Latency (ms)	Patient	40	232	178-338	0.524
			Control	40	227	194-308	
	N200	Amplitude (mV)	Patient	40	20.5	7.3-48	< 0.001*
			Control	40	11.2	2.1-32.2	
	P300	Latency (ms)	Patient	40	350	288-430	0.016*
			Control	40	328	248-369	
	P300	Amplitude (mV)	Patient	40	14.75	7-39	0.019*
			Control	40	11	2.5-32	
Parietal (Pz)	N100	Latency (ms)	Patient	40	99	72-164	0.156
			Control	40	95	65-129	
	N100	Amplitude (mV)	Patient	40	11.75	5.5-25	< 0.001*
			Control	40	5.7	1.4-15	
	P200	Latency (ms)	Patient	40	167	12.8-248	0.543
			Control	40	167	131-217	
	P200	Amplitude (mV)	Patient	40	8.25	2-21	< 0.001*
			Control	40	5.1	1.2-20	
	N200	Latency (ms)	Patient	40	235	22-348	0.641
			Control	40	223	186-306	
	N200	Amplitude (mV)	Patient	40	20.5	4.5-43	< 0.001*
			Control	40	11.3	3.1-34.3	
	P300	Latency (ms)	Patient	40	355	34.8-424	0.020*
			Control	40	331	263-411	
	P300	Amplitude (mV)	Patient	40	12.75	5.5-29	0.012*
			Control	40	10.2	2.6-33.5	

* values are $p < 0.05$.



GRAPH 1. — The patients with IPGE had P300 latency prolongation on the CZ electrode position compared to controls and the patients with SGE.

latency prolongation on FZ electrode position, while the patients with IPGE had P300 latency prolongation on the CZ electrode position (graph 1). The patients with PGE had significantly prolonged latency compared to that of the patients with secondary generalized seizures ($p < 0.05$). P300 latencies were significantly longer in the patients with IPGE than in the normal controls ($p < 0.05$). There was a positive correlation between P300 latencies and the duration of presence of seizures (in years) in the patients with SGE ($p > 0.05$). However, no such correlation was determined in the patients with IPGE. Epileptic patients were categorized as those with normal EEGs, showing epileptiform abnormalities and having slower background activities. When we analyzed the data of these subgroups individually, no statistically significant differences in latencies were determined ($p > 0.05$). The Patients showing epileptiform abnormalities had longer disease duration (in years) than those with slower background activity and than those with normal EEG ($p < 0.05$).

THE EFFECTS OF THE TREATMENT

The patients were treated with VPA, CBZ, DPH, OXC, LMG, TPM and LVT. When the effects of the treatment on event related potential parameters were evaluated, no significant effect was determined ($p > 0.05$). No significant differences in serum levels and mean daily dosage of VPA or CBZ were found in the subgroups classified according to the EEG abnormalities. The patients treated with VPA were grouped based on whether they were receiving VPA as mono or polytherapy. No statistically significant difference was determined between the event-related potential parameters of the patients on VPA as mono or polytherapy ($p > 0.05$). A positive correlation was found present between VPA serum levels (41-101 mg/dl) and latencies of P200 ($p = 0.009$) and N200 ($p = 0.003$) recorded from FZ and CZ electrode positions respectively ($p = 0.050$, $p = 0.031$). The patients treated with CBZ were grouped as those receiving CBZ as mono or polytherapy. No statistically significant difference was determined between the event-related potential parameters of these subgroups ($p > 0.05$). Serum levels of CBZ (4.9-10 mg/dl) and P300 latencies were negatively correlated. However, CBZ dosage (200-1800 mg/day) had no effect on the event-related potential parameters. P300 latencies of the patients receiving VPA and CBZ as monotherapy did not significantly differ. Three of 5 patients who were treated with OXC were receiving their medication as monotherapy. Because of the small number of the patients, the same statistical analysis methods used for previous patients could not be used. Instead, the patients receiving OXC as monotherapy were compared with the patients receiving medication other than OXC and with the normal controls. ERP parameters of the patients receiving OXC, the controls, and those receiving medication other than OXC did not significantly differ ($P > 0.05$). Five patients were receiving LMT, and 3 of them were receiving TPM as polytherapy. Because the number of our patients was small, the same nonparametric tests could not be used for statistical evaluation. Instead, the parameters of the patients treated with LMT and TPM were compared with the other patients who were receiving polytherapy. The P300 latencies of the two groups did not significantly differ ($p > 0.05$).

Discussion

Event related potentials are electric signals from the brain, detected during the performance of various cognitive tasks (9). They have been used extensively in recent years to study brain mechanism underlying cognition and to characterize information processing in normal and disabled population. Studies on ERPs have been conducted focusing especially on the P300 component (3).

P300 is involved in cognitive processing arising from multiple cortical and subcortical areas including particularly the auditory cortex, hippocampus, and amygdale as well as the brainstem and thalamic structures. It is generated when a subject attends to and discriminates between stimulus events which differ from one another along some dimension such as intensity, duration, or modality (9). It has been shown that alterations of AERP components are not specific for any cerebral disturbance and can be found whenever cognitive functions are impaired. It is not known whether these findings constitute an

early prognostic index for cognitive dysfunctions, they possibly indicate slowness in information processing and/or a short term memory disturbance (6).

Some abnormalities in ERP have been described in patients with epilepsy which may be caused by epileptogenic lesion itself, seizures or antiepileptic drug therapy (6), and other factors concerning epilepsy. However, it is difficult to determine which factor is responsible because they are interrelated. Previous reports suggest that the cognitive disturbance in epilepsy mainly originates from epileptogenic lesion itself because the prolongation of the P300 latency is distinctly different between epileptic syndromes and displays characteristic changes with age depending on the epileptic syndrome (10).

Fukae *et al.* showed that the age corrected P300 latency was significantly longer in temporal lobe (TLE) epilepsy compared with idiopathic generalized epilepsy (IGE) and in normal controls (11). Naganuma also reported that the prolongation of the P300 latency was greater in TLE, milder in IGE, and minimal in idiopathic partial epilepsies (IPE) and stated that the cognitive disturbance in epilepsy mainly originated from epileptogenesis itself (12).

Triantafyllou found prolongation of N2 and P3 latencies in epileptics. TLE group was found to have significantly prolonged latencies compared to IGE group and frontal lobe epilepsy group. Nevertheless, this difference was not statistically significant (6).

There is little information as to the correlation between P300 latency and the EEG findings in patients with epilepsy. Triantafyllou *et al.* found that epileptic patients with abnormal EEGs had significantly prolonged P300 latencies compared to ones with normal EEGs (6). Naganuma in his study found no correlation between the P300 latency and the frequency or generalization of paroxysmal discharges and suggested that only the temporal foci might affect the P300 latency (10). Similarly in our study, no correlation was detected between EEG abnormalities and P300 latencies. Background activity on EEG is thought to reflect a dysfunction or maturation of CNS. Therefore, it is natural that prolongation of the P300 latency is associated with some CNS dysfunction (EEG slowing) in patients with epilepsy. On the other hand, these dysfunctions may not always be parallel because of the weak correlation between P300 latency and EEG slowing (10). Gotman and Marciani reported that the number of paroxysmal discharges does not always reflect the severity of epileptic activity (13). Naganuma *et al.* have stated that the existence of EEG abnormalities has relatively little effect on the cognitive function and the cognitive dysfunction in partial epilepsies mainly originate from other factors such as epileptogenic lesions, AED therapy, and some age related factors (10). Our results indicated no correlation between the frequency of paroxysmal discharges and the P300 latency, which is supportive of their results.

In the present study, the patients with epileptiform abnormalities had longer (mean : 5.57 years) disease duration than those showing background slowing (mean : 2 years) or those with normal EEGs (mean : 0.27 years).

There have been relatively few reports concerning the effect of antiepileptic drug (AED) therapy on cognitive evoked potentials. Previous reports suggested that there is no effect of specific AED's on the latency or amplitude of any component (11, 14, 15). However, Triantafyllou stated that cognitive deterioration is worse in those receiving multiple medications. In Triantafyllou's study, patients on monotherapy showed significantly shorter P300 latencies when compared to those on more than one anticonvulsant. This may reflect better cognitive function of patients on monotherapy. Also, patients with shorter duration of antiepileptic therapy showed less prolonged P300 latencies when compared to those on longer treatment (6). Naganuma found that P300 latency became shorter with discontinuation of CBZ therapy, and P300 latency showed a significant positive correlation with the serum concentration of CBZ, which they suspect was a dose dependent effect. Moreover, they stated that at the initiation of CBZ therapy, the P300 latency showed a constant value or gradually became shorter with age in spite of continuos administration of CBZ (12). No effect of CBZ mono or polytherapy dosage on P300 latency was found in our study. However, serum level of CBZ (4.9-10 mg/dl) and P300 latencies were negatively correlated, which suggests that increased serum levels of CBZ may have a positive effect on cognitive dysfunction. Contrarily, the same correlation can not be established with the daily dosage of CBZ. This may imply that the serum level but not the daily dosage has a major impact on cognitive processing.

Panogopoulos has shown that while CBZ monotherapy has no effect on P300 latencies, VPA has a prolonging effect (16). In contrast, Enoki has found that while CBZ monotherapy has a prolongation effect on P300 latency, VPA monothereapy has no effect (17).

VPA treatment (daily dosage and serum levels) did not affect the P300 latencies in our group. In the present study, when patients receiving VPA and CBZ as monotherapy were compared with each other, their P300 latencies were not significantly different.

Because the patients receiving OXC, TMP and LMT were small in number, it is hard to determine whether these treatments have a definite effect on P300 latency.

AERPs may be a suitable method for objective judgement and to follow the cognitive disturbance in patients with epilepsy. They appear to be more sensitive than behavioral measures as significant

changes in ERP have been found in the absence of overt behavioral effects. As was in the earlier studies, we believe this technique may facilitate detection of early effect on central information processing, compatible with a reduction of processing resources and increased effort for a given task (18).

The prolongation of P300 latencies both on PGE and SGE was one of the major abnormalities in this study. The latency prolongation was more evident in our patients with primary generalized seizures than those with secondary generalized seizures. The differences in our results in comparison to previous studies may be due to various factors. Daily dosage, serum levels, numbers and duration of antiepileptic drugs, though at a statistically insignificant level, may have an overall effect on event related potentials. Considering the effect(s) of these factors on ERP parameters, it is not surprising to find conflicting results in different epileptic subgroups of different studies.

In conclusion, ERP and especially latencies of ERP may have an important role in evaluation of subclinical cognitive dysfunction in patients with primary and secondary generalized seizures treated with antiepileptic drugs even though our patients did not have any clinical cognitive dysfunction. On the other hand, whether these patients with P300 abnormalities will show clinical cognitive dysfunction in the future remains uncertain. Long term follow-up studies with larger series of patients are needed to confirm and settle this issue.

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