Original Article

Electrophysiologic Study of Cognitive Functions in Epileptic Patients

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Summary:

Background: Cognitive dysfunctions in epileptic patients may develop due to the neurophysiologic changes related to seizures or antiepileptic drugs.

Objectives: The aim of this longitudinal study was to evaluate the cognitive dysfunction in epileptic patients under antiepileptic drug therapy by the aid of event related potentials.

Patients & Method: P300 latencies were obtained from Fz, Cz and Pz electrodes positions from both epileptic patients (n = 224) and age and sex matched control group (n = 91). Epileptic patients were classified either having partial epilepsy, generalized epilepsy or both partial and generalized epilepsy (combined epilepsy). EEG and p300 test repeated for each patient every three months for one year. The effect of epilepsy type and duration, treatment types (monotherapy/ polytherapy), daily dosages 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 patients with generalized and combined epilepsy as compared to those with partial epilepsy ($P < 0.05$).

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

Key words: p300, cognitive function, epilepsy, electrophysiologic study.

Introduction:

Epilepsy defined basically as an intermittent recurrent derangement of the nervous system presumably due to a sudden, excessive, asynchronous discharge of cerebral neurons [Allan & Robert 2005].The discharge may result in an almost instantaneous loss of consciousness, alteration of perception or impairment of psychic function, convulsive movements, disturbance of sensation or some combination of the above. **Seizure** from the latin word (sacire: "to take possession of") is a paroxysmal event due to abnormal excessive hypersynchronous discharges from an aggregate of central nervous system neurons. This abnormal neuronal activity can have various manifestations ranging from dramatic convulsive activity to experiential phenomena not readily discernible by an observer [Daniel 2006]. Seizures have been classified in several ways according to their supposed etiology, the international classifications of seizures which is based on the clinical form of seizures and its electrophysiologic EEG features has been adopted worldwide because of easy applicability to patients with epilepsy. **Cognitive function** means the ability to use and integrates basic capacities such as perception, language, actions, memory and thoughts. A computer techniques have evolves for examining the processing of information in human brain at a physiological level [Samuel 1985]. A small phasic brain potentials can be detected by means of non invasive procedures and they represent a reflections of patterned neuronal activities associated with informational transactions in the brain, these called event related potentials "ERP" [Steven and Marta 2004]..

Cognitive behavioral problems were recognized in patients with epilepsy in ancient times and documented in the 19TH century neuralgic literatures. Although some patients demonstrate normal intellect and pattern of behavior, some have interictal abnormalities in various cognitive domains such as reduced intelligence & attention, problems in memory, language and frontal executive functions [Marry, Irene & Lucyana 2002].. Longitudinal studies that track cognitive changes in patients with epilepsy have provided proof that intellectual decline is indeed progressive, many studies show that frequent seizures, even when these are short in duration and with subtle symptomatology, can have a substantial impact on daily life and can lead to state-dependent learning impairment [Oostrom, Smeets & Kruitwagen 2003].

So, since cognitive function is a affected in patients with epilepsy but this effect pass unnoticed by most physician and forgotten during the management of epilepsy, and because of the controversy about the real causative factor which contribute to this negative effect on cognition weather it's the epilepsy itself (type, duration, seizure frequency), underlying brain pathology or the use of AEDs. We aimed in this study through studying cognitive function in newly diagnosed epileptic patients using event

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related potentials (p300 latency assessment) to confirm the existence of negative effect of epilepsy on cognitive function, weather good control of seizure by proper use of AEDs (monotherapy drug regimen adjusted according to body weight, clinical condition and EEG finding with avoiding of toxic doses) will improve or diminish cognitive function & if seizure type affect cognitive function.

The aim of this longitudinal study was to evaluate the cognitive dysfunction in epileptic patients under antiepileptic drug therapy by the aid of event related potentials.

Patients and methods:

This is a prospective study conducted in the period from December 2009 to February 2011 in order to evaluate the effect of epilepsy on cognitive function. EEG exam and cognitive function test (p300) was done for each patient four times at three months interval period, and one time for control group. Two hundred twenty four (224) patients included in this study with age range from (12-40) years. We exclude patients below the age of 12 years because of difficulty in conducting the p300 procedure in pediatric age group. All patients are newly diagnosed as having epilepsy, none of them took any medication that may cause epilepsy or on AEDs. After being carefully examined by senior neurologist, brain MRI imaging was done for them. Any patient proved to have a brain lesion was excluded.. Cognitive function test (p300) and EEG exam were done for all patients. The type of patient seizure was determined according to revised criteria of international classification of epileptic seizures [Daniel 2006] depending on EEG findings and clinical attacks of seizures. The suitable AEDs were given by senior neurologist for each patient depending on his body weight and seizure type. During the second, third and fourth visits which was at three months interval, EEG and p300 test was done for all patients. All patients informed about the aim of the study and their acceptance was obtained for children the acceptance of their parents obtained. Control group consist of 91 subjects with age range from 12-40 years. they all were examined by a senior neurologist and show no signs of neurological illness. They were informed about the test and aim of the study and their acceptance was taken. EEG and p300 test was done for all of them. EEG exam was done by using computerized Micromed EEG system 98 device. The patient is seated relaxed and lie comfortable at 45° on the couch. The elastic cap was placed properly over the head. The electrodes were placed on the scalp after being cleaned with rectified spirit and according to the international 10-20 system held in place by the elastic cap, twenty one electrodes used, Then we asked the patient to relax and close his eyes, electrode impedance was kept below 20kΩ. The recording period continued for 30 minutes during which we used hyperventilation (3mints deep breath 17C/mint) and photic stimulation as activation procedures. The recorded EEG waves were averaged, amplified and filtered with band frequencies of 0.5-30 Hz, sweep speed 15second/page and sensitivity of 50uv/cm. The EEG trace is saved for reanalysis. For cognitive function test (P300), computerized Micromed EMG/EP system plus Myoquick was used for studying P300 evoked response, and contains acoustic stimulation connected to cup surface electrodes (Agcl) with 90cm cable, and touch proof connector (ELTPCO), the electrodes were attached to the scalp after its cleaning with rectified spirit. They placed in Fz, Cz, Pz sites according to 10-20 international system of EEG electrode placement using adhesive paste EP (MT60) paste [Micheal 2005], two linked mastoid process electrodes (M1 & M2) serving as reference electrodes, and one forehead (FPz) electrode serve as ground electrode. The electrode impedance was kept below 5kΩ. For acoustic stimulation, a calibrated headphone with minidin connector was used (EPCAP mini). To obtain event related potentials, auditory discrimination tasks "Odd ball" paradigem was used. Two types of tones were delivered binaurally a non target (frequent 1000Hz tone) versus a target (non frequent 2000Hz tone), through a headphone. The sound pressure is 85db for target tone, and 70db for non target tone with a 10msec rise/fall and 40msec plateau time. We ask him to relax with eyes opened and fixed to a specific point in the wall (red paper in the wall) to avoid excessive eye blink. The room was quiet and dimly light. We asked him to count silently the target (infrequent tones). 50 trials were amplified, filtered and averaged in 10 mints recording time (because of difficulty in maintain subject attention for longer periods, First positive peaks following stimulation identified as P200, and the highest positive peak following P200 among the potentials between 250-500msec identified as P300. The test was repeated at least two times to check for reproducibility of the response.

ANOVA and Students t-test were used for comparison.

Results:

Both patients and control subjects divided in to three age groups, **Group 1(GI)**: this age group include subjects from age 12-15 years, **Group 2 (GII)**: this age group include subjects from age 16-18 years & **Group 3 (GIII)**: this age group includes subjects from age 18-40 years. We found a highly significant difference in mean P300 latency between patients with epilepsy and control subjects in the first visit (p value <0.01). and after 12 months of treatment with AEDs the difference in mean p300 latency become non significant in patients below 15 years of age (mean p300 latency was **325.44±18.9**) and (p.value >0.05), but in the second age group the difference in mean p300 latency remain significant even after 12 months of treatment (p.value <0.05) and mean p300 latency was **(308.4 ±15.2)** as compared to that of age matched control subjects which was **(307.23±11.98)** table (1)**.** We divide

patients in to three main categories according to seizure type, partial seizure, generalized seizure & combined seizure: this group of patients have two or more seizure types.

Table (1). Comparison of mean P300 values between patients and control subjects.

Age group	subjects	V1		V2		V3		V4	
		Mean P300	No.	Mean P300	No.	Mean P300	No.	Mean P300	No
GI	patient	373.9± 22.5	75	358.64 ±23.4	75	340.30±21.6	66	325.44 ±18.9	64
	control	325.3± 17.8	32	325.34 ±17.8	32	325.34±17.8	32	325.34 ±17.8	32
	P.value	H.S		H.S		H.S		N.S	
GII	patient	373.30±25.9	91	352.63 ±25.6	91	326.8± 23.6	82	308.4 ±15.2	78
	control	307.23 ±11.98	35	307.23 ±11.98	35	307.23 ±11.98	35	307.23 ±11.98	35
	P.value	H.S		H.S		H.S		S	
GIII	patient	355.35 ± 38.5	43	335.47 ± 31.9	43	316.12 ±25.4	40	306.31 ±19.37	36
	control	297.96 ±14.7	24	297.96 ±14.7	24	297.96 ±14.7	24	297.96 ±14.7	24
	P.value	H.S		H.S		H.S		N.S	

Table (1) show comparison of mean P300 values between patients and control subjects in each visit. GI: a highly significant difference was found in mean P300 values between patients and control group in V1, V2,V3, except in V4 whereas no significant difference obtained.GII: a highly significant difference was found in mean P300 values between patients and control group in V1, V2,V3, but in V4 significant difference still persist. GIII: a highly significant difference was found in mean P300 values between patients and control group in V1, V2, V3, except in V4 whereas no significant difference obtained.

H.S: highly significant difference p.value <0.01, S: significant difference p.value <0.05, N.S: no significant difference, p.value > 0.05. No significant difference found in mean p300 latency between patients with partial epilepsy below age of 16 years as compared to those with generalized epilepsy in the first and second visits and a significant difference found in third and fourth visit. But in patients of age 16-18 years a significant difference found in mean p300 latency in 1st visit only and then the difference become non significant in subsequent visits as illustrated in the table (2).

Table (2): Differences in mean P300 values for patients with partial epilepsy and generalized epilepsy.

Age group	subjects	1st visit		2nd visit		3rdvisit		4thvisit	
		No.	Mean P300	Mean P300	No.	Mean P300	No.	Mean P300	No.
GI	Partial	35	366.3±26.8	351.2 ±25.8	35	332.03 ±22.4	31	319.1 ±16.1	30
	Generalized	23	376.6±14.1	360.2 ±20.4	23	344.95 ±17.72	21	329.5 ±18.7	20
	P.value	N.S		N.S		S		S	
GII	Partial	52	367.69 ±29.7	345.63 ±25.56	52	321.70 ±21.8	47	305.9 ±13.6	45
	Generalized	25	381.04 ±19.1	357.44 ±25.37	25	329.48 ±26.2	23	312.2 ±16.8	22
	P.value	S		N.S		N.S		N.S	
GIII	Partial	34	356.76±34	340.59 ±32.8	34	319.50 ±26.9	32	309.3 ±20.35	29
	Generalized	6	362.33 ±62.1	314.33 ±19.2	6	299.20 ±8.9	5	292.8±5.9	5
	P.value	N.S		N.S		N.S		N.S	

Table (2) show differences in mean P300 values for patients with partial epilepsy and those with generalized epilepsy in different visits.

GI: no significant differences found in first and second visits, but a significant difference found in third and fourth visits.**GII:** a significant difference found in first visit, with no significant difference in second, third and fourth visit. **GIII:** no significant difference found in all visits.

We also found differences in mean P300 values for patients with partial epilepsy as compared to those with combined epilepsy in all visits. In (GI) highly significant difference found in all visits except in fourth visit a significant difference reported, in (GII) no significant difference found in first visit, highly significant difference found in second and third visits, a significant difference found in fourth visit, in (GIII) no significant difference found in all visits table (3).

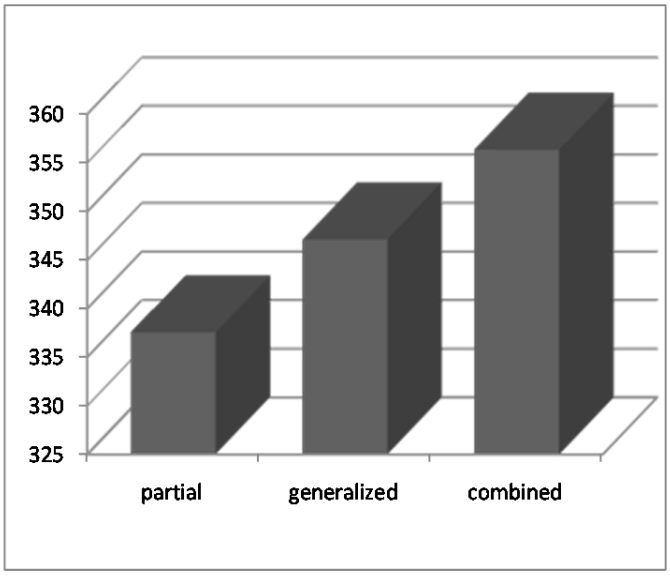

Fig (1): The relation between type of epilepsy and mean P300 values of patients with epilepsy.

Table (3): differences in mean P300 values for patients with partial epilepsy & combined epilepsy.

Age group	subjects	V1		V2		V3		V4	
		No.	Mean P300	Mean P300	No	Mean P300	No.	Mean P300	No.
GI	Partial	35	366.3±26.8	351.2 ±25.8	35	332.03±22.4	31	319.1 ±16.1	30
	Combined	17	386.1±15.52	371.9±15.6	17	351.6±19.2	14	331.7 ±22.1	14
	P.value	H.S		H.S		H.S		S	
GII	Partial	52	367.69±29.7	345.63 ±25.56	52	321.70 ±21.8	47	305.9 ±13.6	45
	Combined	14	380.3 ±15.8	370 ±15.9	14	341.67 ±18.7	12	317.8 ±14.7	11
	P.value	N.S		H.S		H.S		S	
GIII	Partial	34	356.76±34	340.59±32.8	34	319.50 ±26.9	32	309.3 ±20.35	29
	Combined	3	325.3±29.9	319.7±24.95	3	308.3±13.8	3	296 ±1.4	2
	P.value	N.S		N.S		N.S		N.S	

When we do comparison in mean p300 latency between patients with generalized and combined epilepsy, no significant difference found in all visits and p.value >0.05.

A relation between mean P300 latency values for patients with partial, generalized and combined epilepsy was found. Patients with combined epilepsy has the highest mean p300 latency (356.35±19.35) while patients with partial epilepsy has the lowest mean p300 latency (337.55± 13.98 msec) as shown in figure (1).

Discussion:

Cognitive impairment is an important co morbidity of epilepsy, many researches characterize the relationship between cognitive status and a variety of epilepsy factors including etiology, age of onset, seizure types, severity and duration and AEDs **[**Herman *et al*., 2010**].** we found a highly significant difference in mean P300 value for patients with epilepsy as compared to control group in first, second and third visit (p.value <0.01). These findings consistent with that reported by [Aldenkamp & Bodde, 2005] when they study P300 latency in school children with epilepsy and found significant prolongation of mean P300 latency in all epileptic patients as compared to age matched control group. But we found a non significant difference in mean P300 value of epileptic patients as compared to control group in the fourth visit and after twelve months of treatment with AEDs, monotherapy drug regimen used and the dose changed according to clinical condition and EEG results by senior neurologist. So there was

improvement in cognitive function and 152 patient (85.4%) regain a normal P300 value as compared to control group and 26 patients (14.6%) still have prolonged mean P300 latency as compared to control group. These results suggest that epilepsy greatly affect cognitive function of patients and after proper treatment with AEDs the cognitive function can be improved, These findings consistent with that reported by [Fukai *et al.*, 2008] who study P300 value in patient with epilepsy and repeat the test after 16 weeks of treatment with AEDs and found significant reduction in mean P300 latency after treatment with AEDs.patient with partial epilepsy in the first and second age group (patient <18 years old) show highly significant difference in mean p300 latency as compared to control group in the first nine months of treatment and no significant difference after twelve months of treatment. But patients <16 years of age show more rapid reduction in mean p300 latency and their results demonstrate a non significant difference in mean p300 latency since third visit, i.e., after nine months of treatment. And the results of patients in the third age group (>18-40 years) show significant difference when compared to control group even after 12 months of treatment. Beside that no significant difference found in mean p300 latency between patients with generalized epilepsy and control subjects after twelve months of treatment in all age group. Comparison of mean p300 latency for patients of two seizure types with control subjects in the first age group (12-<16 years old) show no significant difference in mean p300 latency (p.value >0.05) even after twelve months of treatment with AEDs. These results could be explained by the presence of a difference in duration of epilepsy although all patients experienced their clinical attacks for the first time but subclinical attacks might be exist long time earlier and affect the cognitive function before clinical attacks [Ronit 2005 & Shery 2009]. Also the brain structures and in fact the mechanisms that mediate cognitive function in children is differ from that of adult and the negative effect of epileptic discharge could be more reversible than adult population. Once more these results suggest that the response to treatment in adult population regarding improvement in cognitive function is delayed as compared to that in children and adolescent . And it also support the theory which assume that subclinical attacks might precede the first clinical attack by longer time and cause a cumulative burden effect on cognitive function which call for longer duration in order to be reversed [Aldenkamp & Arends 2004] especially the effect of transient cognitive impairment (TCI) and the undetected seizures which frequently occur and pass unnoticed by patients but exert a negative effect on behavioral as well as cognitive abilities [Cornaggia 2006]. And the mean p300 latency for patients with partial epilepsy show highly significant difference when compared to patients with combined epilepsy in all visits even after twelve months of treatment and the difference in favor of less mean p300 latency among patients with partial epilepsy. furthermore the comparison between patients with generalized and combined epilepsy show no significant difference in mean p300 latency in all visits, although the mean p300 latency for patients with generalized epilepsy (317.5±20.5) which was more reduced as compared to that of patients with combined epilepsy (323.4±20.9) but still the difference was not significant. These results suggest that patients with partial epilepsy show more reduction in p300 latency which means better cognitive function as compared to that of patients with generalized and combined epilepsy. These findings consistent with that reported by Dr. Omaima who study p300 latency in patients with partial and generalized epilepsy and found a significant reduction in mean p300 latency in patients with partial epilepsy as compared to those with generalized epilepsy [Omaima 2004]. That could be attributed to the role of mesoencephalic reticular formation and the thalamus in the genesis of generalized epilepsy, so any dysfunction in these systems may contribute to the prolongation of p300 latency in patients with idiopathic generalized epilepsy [Lothma 1993].

Conclusion:

Epilepsy even in recently diagnosed epileptic patients has negative effect on cognitive function. Proper use of AEDs (monotherapy drug regimen) with adjustment of the dose according to clinical condition, EEG findings and body weight and avoiding toxic doses will improve cognition in epileptic patients. Early treatment of epilepsy will prevent long term cognitive deficits. Patients with partial epilepsy show better cognitive function than patients with generalized and combined epilepsy. Patients with single seizure type have better cognitive function than patients with two or more seizure type. Seizure type and duration are important causative factors in cognitive deficit in epileptic patients.

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