Original Article

Treatment Of Subclinical Epileptic Discharges Affects Cognitive Functions In Epileptic Patients.

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Summary:

Background: EEG recording showed a definite relationship between epileptiform EEG discharges and cognitive impairments (transient cognitive impairment "TCI"), since interictal spikes, which correspond to a large intracellular depolarization with evoked action potentials, in many ways mimic a "miniseizure." Interictal spikes can result in transitory cognitive impairment with the type of deficit dependent on where in the cortex the spike arises. The interictal spikes, particularly if frequent and widespread, can impair cognitive abilities, through interference with waking learning and memory, and memory consolidation during sleep.

Objectives: the aim of this study is to evaluate the effect of subclinical epileptic discharges on cognitive function in patients with epilepsy.

Patients & Methods: This is a prospective study conducted in Basra teaching hospital in the period from December 2009 to February 2011 in order to evaluate the effect of epileptic discharge 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. the EEG obtained after 30 mints of recording was categorized in to three groups frequent, infrequent and normal EEG record.

Results: we found that patients with frequent IEDs have high mean P300 latency when compared to patients with infrequent and normal EEG exam, also the mean p300 latency significantly reduced (more improvement in cognitive function) after treatment with AEDs.

Conclusion: Treatment of patients with frequent epileptic discharge improve cognitive function in patients with epilepsy, and reduction of IEDs greatly improve cognitive abilities in epileptics.

Key word: cognitive function, interictal epileptic discharge, epilepsy.

Introduction:

A considerable group of about 30% of patients with epilepsy have low average intelligence and inferior academic achievement(1). Vulnerable neuropsychological areas predominantly affect attention, short term memory and cognitive information processing maybe affected by epileptic discharge(2). The interindividually varying cognitive deficits are attributed to the type of epilepsy, to the frequency of seizures, kind and dosage of medication, the extent and the quality of underlying CNS affection as well as to the age at onset(3). A general increased risk for cognitive dysfunction is predominantly seen in those patients suffering either from symptomatic epilepsy, as it is the case in the majority of patients with complex-partial epilepsy, and/or from various types of seizures occurring simultaneously(2,3). This study is to discuss whether interictal epileptiform EEG discharges (IED) in patients with epilepsy may represent an additional risk for cognitive deficit. This assumption is based on the observation that IED may be simultaneously accompanied by transient cognitive impairment (TCI) which itself may contribute to the general long term risk for cognitive development in epilepsy(4).

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This TCI-concept implies a potential risk for the cognitive deficit in patients with epilepsy. One question that has been discussed in this vein is whether the higher rate of learning problems in those 30% of patients with epilepsy needing specific education, may also be the result of interictal epileptic discharge (e.g. spike- and sharp-waves with/without slow waves) occurring simultaneously with TCI's.(5). Focal and generalized IED can also be found in children without epilepsy but with neuropsychological deficits (e.g. regressive speech development). It has thus been discussed whether IEDs are generally associated with an impairment of cognitive CNS functions (e.g. speech, attention) irrespective of whether epilepsy is present simultaneously(4,5)..

Subjects and methodology:

This is a prospective study conducted in Basra teaching hospital in the period from December 2009 to February 2011 in order to evaluate the effect of epileptic discharge 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. 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. The type of patient seizure was determined according to revised criteria of international classification of epileptic seizures(6) 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 were at three months interval, EEG and p300 test were 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 was 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. 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 (3 minutes deep breath 17C/ minutes) 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. The EEG obtained after 30 mints of recording was categorized in to three groups:

1.Frequent: patients with EEG record contain more than 50 bursts of IEDs/30mints.

2.Infrequent: patients with EEG record contains less than 50 bursts of IEDs/30mints.

3. Normal: patients with normal EEG record.

This classification was conducted by Janszky and colleagues in their study for evaluation of patients with epilepsy [Janszky etal 2005]. 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**(7)**, 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 mini-din connector was used (EPCAP mini). To obtain event related potentials, auditory discrimination tasks "Odd ball" paradigm 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 minutes 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:

In this study we found in the first visit, patients with frequent epileptic discharge were 129 (60.2%), and infrequent epileptic discharge was 83(39.8%), with no patients with normal EEG exam. In second visit after three months of treatment with regular AEDs, the number of patients with frequent IEDs was 67(32%), and those with infrequent IEDs was 109 (52%), and those with normal EEG record become 33 (15.9%). So there is about 50% reduction of IEDs from frequent to infrequent with increase in number of patients with normal EEG record (table 1). In the fourth visit and after twelve months of regular treatment with AEDs, we found that only nine patients (5.1%) remains with frequent IEDs, and 41patinets (23%) have infrequent IEDs and 128 (71.9%) gain normal EEG record. When we link the frequency of IEDs with mean P300 latency we found a positive relationship (figure 2), and in patients with frequent IEDs the mean P300 latency was (380.6 ±18.917) in the first visit and gradually decline with subsequent visits to become (336.67±19.2) in the fourth visit (after 12 months of treatment with AEDs but still it shows highly significant difference when compared to control group (table 2). And patients with infrequent IEDs show mean P300 latency of (353.4 ±33.13) in first visit and reduced gradually to become (325.34±24.32 msec) in fourth visit with still highly significant difference when compared to control group (P.value <0.01).

For patients with normal EEG exam their number gradually increased with subsequent visits to become 128 patients in fourth visit and with mean P300 latency of (309.36± 14.2) and with no significant difference when compared to control group (P.value>0.05). When we compare the mean P300 latency for patients with frequent, infrequent and normal EEG exam between visits we found highly significant reduction in mean p300 latency in each visit as compared to previous visit (table 3).

Table (1): Number & percentage of patients with normal, frequent and infrequent epileptic discharge in each visit.

	V1		V2		V3		V4	
	No.	%	No.	%	No.	%	No.	%
Frequent	126	60.2%	67	32.1%	13	6.9%	9	5.1%
Infrequent	83	39.8%	109	52%	87	46.3%	41	23%
Normal	0	0%	33	15.9%	88	46.8%	128	71.9%
Total	209		209		188		178	

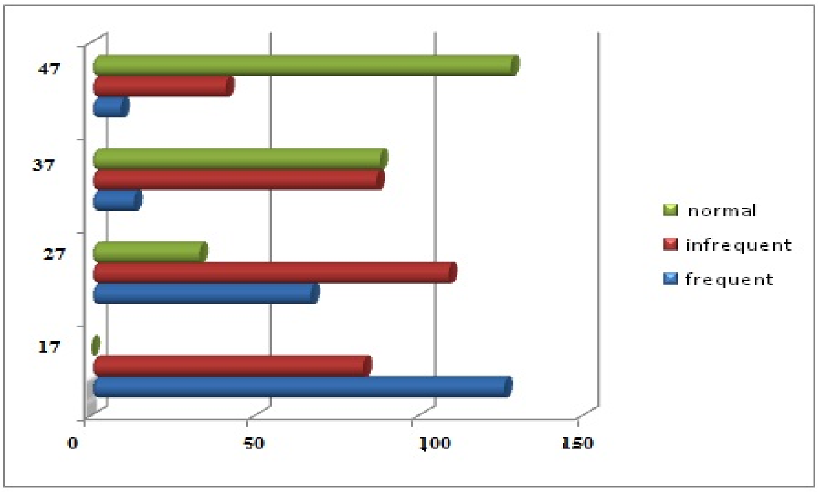

Figure (1) show number of patients with frequent, infrequent and normal EEG exam in each visit. We found gradual reduction in number of patients with frequent epileptic discharge in each visit with increase in number of patients with infrequent and normal EEG exam.

Table (2) show mean P300 latency for patients with frequent, infrequent and normal EEG exam in each visit.

Frequency of epileptic discharge		V1		V2		V3		V4	
		No	Mean P300	No	Mean P300	No	Mean P300	No	Mean P300
Frequent	Patients	126	380.6 ±18.917	67	371.75±15.283	13	357.31±16.5	9	336.67±19.2
	Control	91	311.2 ±18.52	91	311.2 ±18.52	91	311.2 ±18.52	91	311.2 ±18.52
	P.Value		H.S		H.S		H.S		H.S
Infrequent	Patients	83	353.4 ±33.13	109	346.63±26.9	87	337.9±26.3	41	325.34±24.32
	Control	91	311.2 ±18.52	91	311.2 ±18.52	91	311.2 ±18.52	91	311.2 ±18.52
	P.Value		H.S		H.S		H.S		H.S
	Patients	0	0	33	324.9 ±18.37	88	316.60± 16.0	128	309.36± 14.2

Normal	Control	91	311.2 ±18.52	91	311.2 ±18.52	91	311.2 ±18.52	91	311.2 ±18.52
	P.Value				H.S		S		N.S

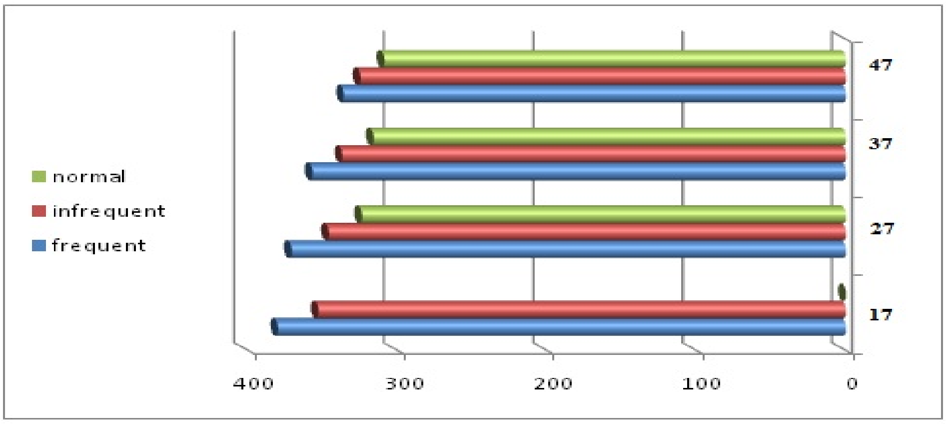

Figure (2) illustrate the relation between frequency of epileptic discharge and mean P300 values of patients with epilepsy, patients with frequent epileptic discharge has highest mean P300 values while patients with normal EEG has the lowest mean P300 value. Also the mean P300 latency of patients with frequent epileptic discharge gradually decline in each visit as their number decrease and the number of patients with infrequent and normal EEG exam increase.

Table (3) comparison in mean P300 latency for patients with frequent, infrequent and normal EEG exam between visits.

Visits	Frequent		Infrequent		Normal	
	NO.	Mean P300	Mean P300	NO.	Mean P300	NO.
V1	126	380.6 ±18.917	353.4 ±33.13	83	0	0
V2	67	371.75 ±15.28	346.63±26.9	109	324.9 ±18.37	33
P value	H.S		H.S		H.S	
V2	67	371.75 ±15.28	346.63±26.9	109	324.9 ±18.37	33
V3	13	357.31±16.5	311.2 ±18.52	87	316.60± 16.0	88
P value	H.S		H.S		H.S	
V3	13	357.31±16.5	311.2 ±18.52	87	316.60± 16.0	88
V4	9	336.67±19.2	325.34±24.32	41	309.36± 14.2	128
P value	H.S		H.S		H.S	
V1	126	380.6 ±18.917	353.4 ±33.13	83	0	0
V4	9	336.67±19.2	325.34±24.32	41	309.36± 14.2	128
P value			H.S			

Discussion:

we found that patients with frequent epileptic discharge after proper treatment with AEDs show significant reduction in mean P300 latency as compared to their mean P300 latency in first visit, and as the number of patients with normal EEG exam increase their p300 latency gradually decline and in fourth visit it show no significant difference from that of control group, so as the frequency of IEDs increase P300 value also increase which mean a reduction in cognitive function and as the frequency of IEDs reduced or the record become normal P300 latency reduced which indicate improvement in cognitive function. These results suggest that treatment of patients with epilepsy should put in concern reduction or even treatment of IEDs since it affect cognitive function and it may cause transient cognitive impairment and behavioral as well as psychological problems especially in children with epilepsy (9). These findings could be related to the fact that at cellular level since epileptiform discharges generating neurons exhibit increased susceptibility to premature death so early detection of IEDs and appropriate treatment can prevent further neuronal damage (10,9). Also as the dose of AEDs adjusted according to EEG results, the frequency of IEDs decline with more control of seizure and good reduction in clinical attacks. These results agree with that of [Binnie etal 2003] in his study about treatment of patients with epilepsy in view of EEG monitor(11,12) , and he found that after 6 months of treatment with regular AEDs, 75% of his patients show good clinical control and 61.5% of them show normal EEG record. Although some other studies show no relation between clinical control of epilepsy and EEG findings(13) ,but this study conducted only in patients with mesial temporal sclerosis, and this group of deep seated foci are difficult to be recorded by scalp electrodes, also those patients have a structural lesion that may affect the results (act as source for continues IEDs), but in our study we choose patients with normal MRI and CT scan to exclude any possible structural brain abnormalities. These results suggest that proper choose of AEDs according to seizure type and regular administration, beside adjustment of the dose according to clinical condition of the patient will help greatly in reduction of IEDs (14). Beside that management of epilepsy can be aided with continues EEG monitor for epileptic discharge and clinical as well as EEG control of epilepsy and IEDs if combined together will achieve good control of both clinical and subclinical seizures (15).

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