



Research Article

The Effect of Anti-epileptic drugs on Visual Evoked Potential in Patients with Generalized Tonic-clonic Seizures: A Prospective Case-controlled Study

Alshareef Aysha* and Dandachi Nadia

Abstract

Objective: The main purpose of the present study was to determine whether anti-epileptic drugs induce any abnormal changes in the visual evoked potential (VEP) patterns.

Methods and material: This prospective case controlled study was done at the Neurology Department of King Abdulaziz University Hospital, Jeddah, Saudi Arabia (between January 2013 and December 2014). The study subjects were divided into cases and controls; with the case group subjects being those epilepsy patients receiving antiepileptic drugs. Using the Visual Evoked Potentials (VEPs), control and case subjects were compared with respect to the values of: Latency N75, Latency P100 and Amplitude P100.

Results: A statistically significant difference was seen between the controls and the subjects receiving antiepileptic double and triple drug therapy; with respect to the value of Latency P100 (P-value 0.042 and 0.044 respectively). The analysis of variances (ANOVA) revealed a statistically significant difference (P-value 0.007 and 0.038) with respect to the mean scores of Latency N75 and the mean scores of Amplitude P100; in relation to age; between the controls and the case group patients receiving anti-epileptic monotherapy. A statistically significant difference ($p=0.01$) was noted with respect to Latency N75 related to age, between the controls and patients receiving antiepileptic double therapy. A significant difference was also noted in Latency P100 mean scores related to age ($p=0.05$). A gender-wise comparison revealed a statistically significant difference, in the mean scores of Latency P100, with the difference showing a male predilection

Conclusion: Anti-epileptic drugs can induce abnormalities in the VEP patterns. Age and gender are factors that can influence the occurrence of such abnormalities; in relation to the number of anti-epileptic drugs taken by the patients. Future studies are recommended to evaluate the impact of the type and duration of epilepsy, in causing VEP related abnormalities

Keywords

Epilepsy; Anti-epileptic drugs; Visual evoked potential; VER; VEP

Introduction

Visual evoked potential (VEP), visual evoked response (VER) and visual evoked cortical potential (VECP) are similar terms used for referring to electrical potentials, which are generated by visual stimuli. These short stimuli are recorded from the scalp, overlying the visual cortex. By signal averaging, EEG is the method commonly employed to capture and record the VEP waveforms. VEPs are most importantly used to measure the visual pathways' functional integrity from the retina, via the optic nerves, up to the visual cortex in the brain [1]. The visual disruptions which patients with epilepsy experience could be attributable to either their epilepsy itself or to the anti-epileptic drugs they are prescribed to control their seizures [2]. These visual disruptions include constrictions of the visual field, vision deficits, blurred vision, diplopia and nystagmus and altered electrophysiological [1]. Gamma amino butyric acid (GABA) or GABA-receptor blockers are seizure inducers, and many anti-epileptic drugs have GABA enhancing qualities [3]. The enhancement of GABA levels by anti-epileptic medication may affect the cortical response, to stimuli of different spatial frequencies. For example, valproate (VPA) is an anti-epileptic medication that causes an increase in the levels of GABA in the entire brain [4,5]. It has been reported that VPA reduces the P100-amplitude response to patterned stimuli. Some reports from past clinical evidence also state that it increases P100-latencies in epileptic patients [6]. On the other hand, carbamazepine (CBZ), an anti-epileptic drug, doesn't affect GABA transmissions [7] but rather interferes with sodium-dependent action potentials and it has also been reported to prolong P100 latencies [8].

Several studies have been conducted to evaluate the effects of anti-epileptic drugs on the visual pathway by measuring VER. The purpose of the current study was to elicit a possible relationship between VER related abnormalities among epilepsy patients and the number of antiepileptic drugs being taken.

Methods and Materials

This prospective experimental study was carried out at the Outpatient Department of Neurology at King Abdulaziz University Hospital, Jeddah, Saudi Arabia (between January 2013 and December 2014).

The study focused on the following anti-epileptic drugs: Carbamazepine, Valproic acid, Levetiracetam, Topiramate, and Phenytoin. Other drugs were used by a fewer number of patients: Clonazepam, Diazepam, Pregabalin, Lamictal and Lorazepam.

A total of 80 healthy subjects not using any anti-epileptic drugs were chosen for the control group. The control group subjects were recruited from among the laboratory personnel, clinic staff and medical students. Forty-eight subjects were female and 32 were male, with ages ranging from 6 to 97 years old (mean age of 29.6 years).

The case group comprised of 80 epileptic patients who were taking anti-epileptic drugs. The case group subjects were recruited from the Neurology Clinic at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The case group was further divided to three smaller groups comprising of: 1) patients taking only one anti-epileptic drug (mono therapy) 2) patients taking two antiepileptic

*Corresponding author: Alshareef Aysha, Department of Neuroscience, King Abdulaziz University Hospital, Jeddah, Saudi Arabia, Tel: +966 504674409; E-mail: kdraysha@hotmail.com

Received: September 21, 2016 Accepted: October 26, 2016 Published: November 02, 2016

drugs simultaneously (double-therapy) and 3) patients taking three or more anti-epileptic drugs. Forty-eight patients were female and 32 were male, with ages ranging from 5 to 95 years old (mean age of 25.7 years). The epilepsy type was generalized tonic-clonic seizures. Informed consent was obtained from all subjects.

Using the VEPs, the controls and cases were compared with respect to the following recorded variables: 1) Latency values of N75 2) Latency values of P100 3) Amplitude values of P100.

VEPs were recorded from the scalp overlying the visual cortex. EEG was then used to extract the VEP waveforms by signal averaging. The VEPs were primarily used to measure the integrity of the function in the visual pathways [1].

The VEP waves were defined as: an initial negative potential at ~70 ms (N1 or N75), a positive potential at ~100 ms (P1 or P100), and a negative potential at ~145 ms (N2 or N145). See image in the given link. (<https://visionhelp.files.wordpress.com/2011/04/vep-waveform.jpg>).

Results

Table 1 and Figure 1 given below provide a summary of the age-wise distribution of the epileptic patients (cases) and controls included in the study. In (0 to 25) 32.1% control compared to 5.8% patients on triple therapy, 11.5% double therapy, and 12.2% on mono-therapy. In age class (25 to 50), 13.5% control is compared with 3.5% of patients on triple therapy, 3.2% double therapy, and 9.0% on mono therapy. In age (≥ 50), 5.8% control compared with 1.3% double therapy, and 1.9% patients on mono therapy.

Table 2 and Figure 2 describe the gender wise distribution of the epileptic patients (cases) and controls included in the study.

The majority of the study subjects were females (60.9%) whereas males comprised 39.1% of the total study subjects

No statistically significant difference was noted between the control group and the case subgroup receiving antiepileptic mono

therapy; with respect to mode of drug therapy and mean scores of latency. However it was found that there is a statistically significant difference between the control and the group of patients taking 3 or more drugs therapy in terms of Latency P100 ($p=0.044$), as well as between the control group and the group of patients taking a double drug therapy ($p=0.044$). A tab ulated summary of these findings has been presented in Tables 3-5 below.

The ANOVA test was employed to compare between the mean scores of the control group and mono-therapy patients group classified as per age (Table 6). This analysis revealed a statistically significant difference between the mean scores of Latency N75 and Amplitude P100, between the two groups (P-values 0.007 and 0.038 respectively). Furthermore, the significant differences were noted between the younger groups as compared to the older groups (0.002) (Table 7). Upon comparison between the control group versus the group of patients taking 3 or more drugs; a statistically significant difference was noted at the (0.05) level in Latency N75 mean scores related to age (Tables 8 and 9). However, the results did not show any significant differences in Latency P100 and Amplitude P100. When comparing between the control group and the group of patients taking double therapy, the results showed that there is a statistically significant difference at the (0.01) level in Latency N75 related to age (Table 10). There is also a significant difference in Latency P100 mean scores related to age at the (0.05) level.

The control group and the group of patients taking mono-therapy were compared in terms of means scores related to gender (Table 11). The results of t-test showed a statistically significant difference in the mean scores of Latency P100, between the male and female case group subjects. No significant difference was noted with respect to the mean scores of Latency N75 and Amplitude P100. Upon comparing the mean scores of the control group with the group of patients taking a double therapy, in terms of gender; the results again did not show statistically significant difference in the mean scores of latency between male and female subjects (Tables 12 and 13).

Table 1: Summary of age-wise distribution of Epileptic subjects (case group) and control group.

Cases	Age groups						Total	
	0 to 25		26 to 50		50+		f	%
	f	%	f	%	f	%		
Control	50	32.1	21	13.5	9	5.8	80	51.3
Epileptic patients on three or more drugs	9	5.8	6	3.8	0	0.0	15	9.6
Epileptic patients on double-therapy	18	11.5	5	3.2	2	1.3	25	16.0
Epileptic patients on mono-therapy	19	12.2	14	9.0	3	1.9	36	23.1
Total	96	61.5	46	29.5	14	9.0	156	100.0

f = number

Table 2: Summary of gender-wise distribution of Epileptic subjects (case group) and control group.

Cases	Gender				Total	
	Male		Female		f	%
	f	%	f	%		
Control	31	19.9	49	31.4	80	51.3
Epileptic patients on three or more drugs	4	2.6	11	7.1	15	9.6
Epileptic patients on double- therapy	14	9.0	11	7.1	25	16.0
Epileptic patients on mono-therapy	12	7.7	24	15.4	36	23.1
Total	61	39.1	95	60.9		100.0

f= number

Table 3: Summary of differences between controls versus Mono-therapy subjects with respect to latency.

	Study Group				t-test	p-value
	Control (n=80)		Mono-therapy(n=36)			
	Mean	Stdv.	mean	Stdv.		
Latency N75	67.88	11.26	64.52	8.64	1.594	0.114
Latency P100	102.11	10.24	106.34	14.42	-1.805	0.074
Amplitude P100	12.08	8.51	11.74	6.90	0.208	0.836

Table 4: Summary of differences between Controls versus Double-therapy subjects with respect to latency.

	Study Group				t-test	df	p-value
	Control (n=80)		Double therapy n=25)				
	Mean	Stdv.	mean	Stdv.			
Latency N75	67.88	11.26	65.35	7.67	1.048	103	0.30
Latency P100	102.11	10.24	107.51	14.81	-2.056*		0.042
Amplitude P100	12.08	8.51	12.64	6.79	-0.300		0.77

df= degree of freedom

Table 5: Summary of differences between Controls versus Three or more drug therapy subjects in term of latency.

	Group				T-test	df	P-value
	control (n=80)		3 or more drug therapy(n=15)				
	Mean	Stdv.	mean	Stdv.			
Latency N75	67.88	11.26	65.69	12.48	0.681	93	0.50
Latency P100	102.11	10.24	109.30	21.07	-2.046*		0.044
Amplitude P100	12.08	8.51	9.97	3.00	0.947		0.35

df= degree of freedom

Table 6: Summary of the anova analysis of differences related to age with respect to latency and amplitude (Controls versus Mono-therapy subjects).

		Sum of Squares	df	Mean Square	F	p-value
Latency N75	Between Groups	1097.861	2	548.930	5.251*	.007
	Within Groups	11811.736	113	104.529		
	Total	12909.597	115			
Latency P100	Between Groups	366.042	2	183.021	1.322	.271
	Within Groups	15647.351	113	138.472		
	Total	16013.392	115			
Amplitude P100	Between Groups	416.778	2	208.389	3.375**	.038
	Within Groups	6977.840	113	61.751		
	Total	7394.617	115			

*Difference is significant at the (0.01) level

**Difference is significant at the (0.05) level

df= degree of freedom

F= F-statistic

Table 7: Summary of mean scores of latency and amplitude classified as per age-groups.

Age Group		Latency N75	Latency P100	Amplitude P100
0 to 25	Mean	68.5551	104.7036	13.3174
	N	69	69	69
	SD	11.30615	9.75844	9.68270
26 to 50	Mean	66.3971	100.7486	10.9000
	N	35	35	35
	SD	7.62512	10.43870	3.56916
50+	Mean	58.2375	103.8833	7.3925
	N	12	12	12
	SD	10.19140	22.29359	3.92424
Total	Mean	66.8366	103.4254	11.9751
	N	116	116	116
	SD	10.59516	11.80029	8.01879

SD= standard deviation

Discussion

This study focused on analyzing the effects of anti-epileptic medication on the visual responses according to the waves of latency and amplitude.

To the best of our knowledge, we believe that this is the first study conducted to evaluate the effect of anti-epileptic drugs on VEPs, factoring in the correlation between the impact on VEP and number of anti-epileptic drugs being taken. The P100-Latency, N75-Latency,

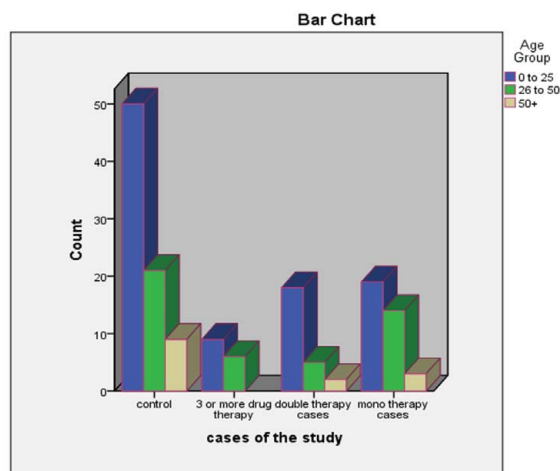


Figure 1: Graphical age-wise distribution of epileptic subjects (case group) and control group.

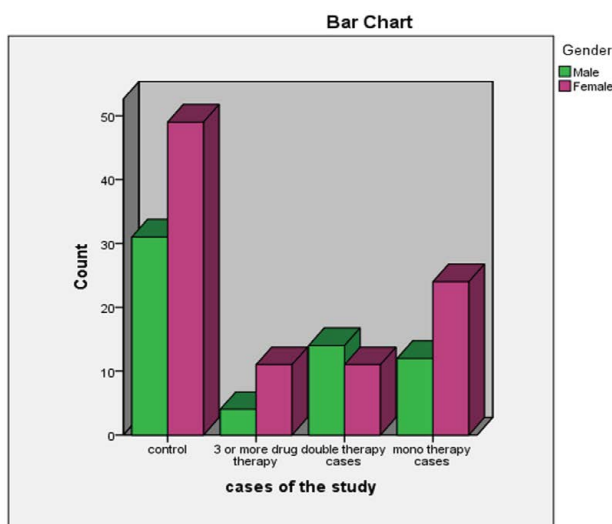


Figure 2: Graphical gender-wise distribution of epileptic subjects (case group) and control group.

Table 8: Summary of comparisons of latency and amplitude with respect to age.

Dependent Variable	(I) Age Group	(J) Age Group	Mean Difference (I-J)	SE	p-value
Latency N75	0 to 25	26 to 50	2.15793	2.12166	.311
		50+	10.31757 [*]	3.19775	.002
	26 to 50	0 to 25	-2.15793-	2.12166	.311
		50+	8.15964 [*]	3.42012	.019
	50+	0 to 25	-10.31757- [*]	3.19775	.002
		26 to 50	-8.15964- [*]	3.42012	.019
Amplitude P100	0 to 25	26 to 50	2.41739	1.63072	.141
		50+	5.92489 [*]	2.45781	.018
	26 to 50	0 to 25	-2.41739-	1.63072	.141
		50+	3.50750	2.62873	.185
	50+	0 to 25	-5.92489- [*]	2.45781	.018
		26 to 50	-3.50750-	2.62873	.185

SE=standard error

Table 9: Summary of mean scores of latency and amplitude related to age.

Age Group		Latency N75	Latency P100	Amplitude P100
0 to 25	Mean	69.4287	105.6860	13.0225
	N	68	68	68
	Std. Deviation	11.23500	12.33678	9.53622
26 to 50	Mean	65.1192	99.5519	11.5577
	N	26	26	26
	Std. Deviation	6.84317	6.98486	3.34305
50+	Mean	59.0955	98.3455	8.7536
	N	11	11	11
	Std. Deviation	8.65227	12.91502	5.26324
Total	Mean	67.2790	103.3981	12.2126
	N	105	105	105
	Std. Deviation	10.53776	11.64632	8.10788

Table 10: Summary of ANOVA analysis of differences in latency and amplitude between controls versus double therapy subjects related to age.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Latency N75	Between Groups	1172.190	2	586.095	5.761**	.004
	Within Groups	10376.434	102	101.730		
	Total	11548.624	104			
Latency P100	Between Groups	1021.396	2	510.698	3.981*	.022
	Within Groups	13084.824	102	128.283		
	Total	14106.220	104			
Amplitude P100	Between Groups	187.364	2	93.682	1.437	.242
	Within Groups	6649.362	102	65.190		
	Total	6836.726	104			

df= degree of freedom
F= F-Statistic

Table 11: Summary of differences between mean scores of control versus mono-therapy subjects related to gender.

	Gender				t-test	p-value
	Male (n=43)		Female (n=73)			
	Mean	Stdv.	mean	Stdv.		
Latency N75	65.84	7.18	67.42	12.18	-0.775	0.44
Latency P100	106.25	11.23	101.76	11.89	2.01*	0.05
Amplitude P100	10.76	5.36	12.69	9.20	-1.25	0.21

Table 12: Summary of differences between mean scores of control versus double-therapy subjects related to gender.

	Gender				T-test	df	P-value
	Male (n=45)		Female (n=60)				
	Mean	Stdv.	mean	Stdv.			
Latency N75	65.90	5.88	68.32	12.94	-1.166	103	0.25
Latency P100	105.65	10.96	101.71	11.94	1.732		0.086
Amplitude P100	11.21	5.19	12.97	9.72	-1.099		0.27

df= degree of freedom

Table 13: Summary of differences between mean scores of controls versus three or more drug-therapy subjects related to gender.

	Gender				t-test	df	p-value
	Male (n=35)		Female (n=60)				
	Mean	Stdv.	Mean	Stdv.			
Latency N75	66.48	6.29	68.15	13.56	-0.687	93	0.49
Latency P100	107.32	14.90	100.87	10.65	2.453*		0.016
Amplitude P100	10.40	4.41	12.53	9.34	-1.30		0.21

df= degree of freedom

and P100-Amplitude comprised the three parameters that were considered.

The generator of VEPs is the occipital cortex. The N1 peaks

are generated in the mesial-lingual cortex and the P100 peaks are generated in the lateral occipital pole [9].

In the present study, a statistically significant difference was noted

terms of prolonged P100 Latency; between the control group and the case group of patients taking a double anti-epileptic drug therapy as well as with the group of patients taking the three or more anti-epileptic drug therapy. However, no statistically significant difference was seen with respect to N75 Latency and P100 amplitude (Tables 3, 9 and 11). More than 90% of the case group patients had generalized tonic-clonic seizures. This implies that the type of epilepsy perhaps cannot be considered as a confounding factor. Prolonged P100 latency in relation to the number of anti-epileptic drugs can perhaps be attributed to the direct effect of the drugs or due to the indirect effect of uncontrolled epilepsy.

It was reported in previous studies that the type of epilepsy as well as anti-epileptic medication have a separate effect on the different VEP components [10]. Several mechanisms were suggested in explaining the effects of anti-epileptic drugs on the VEP patterns. One of the explanations put forth states that valproic acid enhances the γ -aminobutyric acid (GABA)-mediated inhibition and that GABA is also involved in collateral inhibition inside the visual cortex [11]. Another theory explaining the effect of anti-epileptic drugs on VEP waveforms suggests that the acute administration of VPA causes a reduction in the brain levels of the excitatory amino acid aspartate [12]. The action of valproic acid as well as carbamazepine interferes with a neuron's ability to maintain high frequency, repetitive, firing of the sodium-dependent action potentials [13,14].

Previous studies have compared VEP related changes in photosensitive (PS) epilepsy versus non-photosensitive (non-PS) epilepsy in newly diagnosed patients. They concluded that shortened N75 as well as normal P100 latencies in the P-VEPs, with higher than normal P100 amplitudes were detected in PS epileptic patients. In the P-VEPs of non-PS patients, the N75 latencies were not affected. However, the P100 latencies of non-PS patients were prolonged; the P100 amplitudes were not changed. It appears that the VEP findings are influenced; not by the type of epilepsy, but mainly by the presence or absence of photo-paroxysmal responses (PPRs), regardless of the use of anti-epileptic drugs [15].

Prolonged P-VEP peak latencies were reported in different types of epilepsy; including progressive myoclonus epilepsy, partial and generalized seizures, complex partial seizures, as well as other types of epilepsy [16-19].

We conclude from our study that the number of anti-epileptic drugs taken by patients can induce abnormal changes in the VEP waves, in forms of prolonged P100 latency. Further studies are recommended in order to understand the pathophysiological implications of epilepsy types, disease severity and the different types of anti-epileptic drugs.

Acknowledgments

Grants-to-Aid to King Abdulaziz University Hospital and the Neurology Department for their full support.

References

1. Creel DJ (2012) Visually Evoked Potentials.
2. Hilton EJ, Hosking SL, Betts T (2004) The effect of antiepileptic drugs on visual performance. *Seizure* 13: 113-128.
3. De Deyn PP, Marescau B, MacDonald RL (1990) Epilepsy and the GABA-hypothesis, a brief review and some examples. *Acta Neurol Belg* 90: 65-81.
4. Löscher W (1979) GABA in plasma and cerebrospinal fluid of different species. Effects of c-acetylenic GABA, c-vinyl GABA and sodium valproate. *J Neurochem* 32: 1587-1591.

5. Cotariu D, Zaidman JL, Evans S (1990) Neurophysiological and biochemical changes evoked by valproic acid in the central nervous system. *Prog Neurobiol* 34: 343-354.
6. Harding GFA, Alford CA, Powell TE (1985) The effect of sodium valproate on sleep, reaction times, and visual evoked potential in normal subjects. *Epilepsia* 26: 597-601.
7. Macdonald RL (1989) Carbamazepine – mechanisms of action. *Antiepileptic drugs* (3rd Edtn) Raven Press Ltd, New York.
8. Zgorzalewicz M, Galas-Zgorzalewicz B (2000) Visual and auditory potentials during longterm vigabatrin treatment in children and adolescents with epilepsy. *Clin Neurophys* 111: 2150-2154.
9. Arroyo S, Lesser RP, Poon WT, Webber WR, Gordon B, et al. (1997) Neuronal generators of visual evoked potentials in humans: visual processing in the human cortex. *Epilepsia* 38: 600-610.
10. Geller AM, Hudnell HK, Vaughn BV, Messenheimer JA, Boyes WK (2005) Epilepsy and medication effects on the pattern visual evoked potential. *Documenta Ophthalmologica* 110: 121-131.
11. Fought E, Lee SI (1984) Pattern reversal visual evoked potentials in photosensitive epilepsy. *Electroencephalogr Clin Neurophysiol* 59: 125-133.
12. Schechter PJ, Tranier Y, Grove J (1978) Effect of n-dipropylacetate on amion acid concentrations in mouse brain: correlations with anti-convulsant activity. *J Neurochem* 31: 1325-1327.
13. McLean MJ, Macdonald RL (1986) Sodium valproate, but not ethosuximide, produces use- and voltage-dependent limitation of high frequency repetitive firing of action potentials of mouse central neurons in cell culture. *J Pharm Exp Ther* 237: 1001-1011.
14. Franceschetti S, Hamon B, Heinemann U (1986) The action of valproate on spontaneous epileptiform activity in the absence of synaptic transmission and on evoked changes in $[Ca^{2+}]_i$ and $[K^+]_i$ in the hippocampal slice. *Br Res* 386: 1-11.
15. Genç BO, Genç E, Güney F, İlhan N (2005) Pattern-reversal Visual Evoked Potentials in Patients with Newly Diagnosed Epilepsy. *Epilepsia*, 46: 1219-1223.
16. Mervaala E, Keranen T, Paakonen A, Partanen JV, Riekkinen P, et al. (1986) Visual evoked potentials and quantitative EEG in Baltic progressive myoclonus epilepsy. *Epilepsia* 27: 542-547.
17. Mervaala E, Partanen J, Nousianinen U, Sivenius J, Riekkinen P, et al. (1989) Electrophysiologic effects of gamma-vinyl GABA and carbamazepine. *Epilepsia* 30: 189-193.
18. Drake MF, Pakalnis A, Padamadan H, Hietter SA, Brown M (1989) Effect of antiepileptic drug monotherapy and polypharmacy on visual and auditory evoked potentials. *Electromyogr Clin Neurophysiol* 29: 55-58.
19. Cosi V, Callieco R, Galimberti CA, Manni R, Tartara A, et al. (1989) Effects of vigabatrin on evoked potentials in epileptic patients. *Br J Clin Pharmacol* 27: S 61-68.

Author Affiliations

Top

¹Department of Neuroscience, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

Submit your next manuscript and get advantages of SciTechnol submissions

- ❖ 80 Journals
- ❖ 21 Day rapid review process
- ❖ 3000 Editorial team
- ❖ 5 Million readers
- ❖ More than 5000 
- ❖ Quality and quick review processing through Editorial Manager System

Submit your next manuscript at • www.scitechnol.com/submission