

Assessment of the Cognitive function in the epileptic patients and effect of anti epileptic drugs

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Abstract

This study is a prospective study that aimed to evaluate cognitive function in newly diagnosed epileptic patients before and 3 months after taking an antiepileptic drug by doing Wechsler IQ for patients before and 3 months after treatment and for their parents . the study included 40 patients. Divided into 4 groups (each containing 10 patients) and subjected to one of the following AEDs for 3 months : 1. group A : receiving Carbamazepine (Tegretol) in a dose of 10-20 mg/kg/day,2. group B receiving Na valproate (Depakine) in a dose of 20-40 mg/kg/day,3. group C : receiving Lamotrigine (Lamictal) in a dose of 3-5 mg/kg/day,4. group D : receiving Topiramate in a dose of 3-6 mg/kg/day.Taking into consideration other factors that may be of Significance in affecting cognitive functions as seizure frequency ,age at onset of seizures and EEG abnormality. The results of the study were as following:1-There are statistically significant differences between IQs before and after treatment in the 4 groups. 2-there is +ve correlation between IQs before and after ttt in all groups.3- there is -ve correlation between IQs after ttt and frequency of seizures in group (B).4- There is +ve correlation between IQs of parents and patients' IQs before ttt in all groups.5-there is +ve correlation between IQs after ttt and parents' IQs in all group,From these results we can conclude that heredity is the main factor responsible for most of the decline in cognitive functions seen in epileptic patients after treatment with AEDs and other factors as seizure frequency, age at onset of seizures and EEG abnormalities may also play a role, By comparing the four groups we found that the impairment in cognitive function is mainly related to the impairment in cognitive function already present in those patients before the start of treatment. which were correlated and inherited in all groups.

Keywords: Epilepsy,Cognition,Antiepileptic drugs

1. Introduction

In the Around 50 % million people have epilepsy world wide ;it is especially prevalent in childhood , adolescence. Neuropsychological impairment is an important co-morbidity of epilepsy, people with epilepsy can develop behavioral and emotional problems and have an increased risk of poor self-esteem, depression and suicide. (Elger CE et al, 2004). A long and rich history of research has characterized relationships between cognitive status and a variety of clinical epilepsy factors, including etiology, age of onset, seizure type and severity, duration, antiepileptic medications, and other factors (Aldenkamp A, Arends J. 2004). Controlled studies of children and adolescents with chronic epilepsy, but with substantially fewer years of recurrent seizures than the typical chronic adult population, have demonstrated that these patients may exhibit significant neuropsychological impairment (Jones J , et al , 2004) , suggesting the influence of an early adverse neuro-developmental impact on cognition. Psychiatric or behavioral as well as academic problems may antedate the diagnosis of epilepsy not only in children but also in adults with epilepsy (Hesdorffer DC, et al , 2006). Memory impairments have been found to be more prevalent in symptomatic and cryptogenic epilepsies, when compared to idiopathic epilepsy (Klein et al, 2000; Mazzini et al, 2003). Among epilepsy syndromes occurring in children, those associated with cognitive or behavioural impairment include a) tuberous sclerosis which is characterized by autism and seizures (Bergin et al, 2000), b) pediatric epilepsy syndromes associated with mental retardation such as Lennox–Gastaut syndrome, and c) pediatric epilepsy syndromes characterized by prominent behavioral manifestations, such as Landau–Kleffner syndrome, an epileptic encephalopathy of which aphasia is the distinguishing feature (Ribbler et al, 1990). In contrast, idiopathic generalized epilepsies are more rarely associated with obvious or severe intellectual impairment (Giovagnoli et al, 1999). In general, generalized tonic–clonic seizures are associated with greater cognitive impairment than partial seizures, whereas the highest risk is observed with status epilepticus (Rausch et al, 1991). Absence seizures also seem to be associated with lower cognitive performance compared with convulsive seizures . Seizures in temporal lobe epilepsy can damage the brain, and therefore they can negatively affect memory. this is most impressively demonstrated by TLE patients who became global amnesic after a convulsive or non-convulsive status epilepticus (Dietl T. et al. 2004). Antiepileptic drugs produce global changes in the excitation levels in the central nervous system and often lead to cognitive and behavioral deficits. These deficits vary and must be considered independently in every patient.

A number of consistent risk factors have been established. Poly-pharmacy and high blood levels of an antiepileptic drug (AED) increase the risk of cognitive side effects. Different effects have been demonstrated for some AEDs, but comparative data are incomplete across all of them. Other factors such as patient age and type/frequency of seizures may also be important contributors to the patient's cognitive state. AEDs can have positive or negative effects on mood, providing another consideration in choosing the course of treatment. (Meador, et al, 2005). A variety of factors beyond AEDs can affect cognitive function in patients with epilepsy. As a group, epilepsy patients have been shown to perform more poorly than normal controls on a variety of cognitive measures, although some epilepsy patients have superior cognitive abilities, the etiology of seizures is one of the primary determinants of the extent of cognitive impairment. Earlier onset of seizures, for example, frequently leads to more severe cognitive impairments. Seizure type, frequency, severity, and duration and cerebral lesions acquired before or developed as a consequence of seizures also contribute to cognitive function in epilepsy patients. (Carpay JA, et al, 2005)

The effects of AEDs on cognition are especially significant since AEDs are often be selected based on both traditional measures of treatment effectiveness such as efficacy and tolerability, and their negative neuropsychological side effects. The presence of AED-induced cognitive side effects is an important concern of epilepsy patients taking medications (Carpay JA, et al, 2005). Magnitude of AED-related cognitive dysfunction is generally modest in mono-therapy and when the AED is present at therapeutic serum concentrations. However, there are circumstances in which decreased cognitive function assumes greater importance, such as learning in school children, when driving or operating machinery, and when cognitive skills might be especially vulnerable, such as in the elderly (Bourgeois BF, 2004).

PATIENTS AND METHODS

This study is carried out on forty, newly diagnosed, epileptic patients with their ages ranging between 7 and 18 years old who are divided into 4 groups A, B, C and D (each containing 10 patients). Each subjected to one of the following antiepileptic drugs for 3 months, Group (A) : receiving Carbamazepine (Tegretol) at dose of 10-20 mg/kg, Group (B): receiving Na valproate (Depakine) at dose of 20-40 mg/kg, Group (C): receiving Lamotrigine (Lamictal) at dose of 3-5 mg/kg, Group (D): receiving Topiramate (Topiramate) at dose of 3-6mg/kg. All patients evaluated for cognitive functions by Wechsler IQ before and three months after treatment and also by subjecting their parents for Wechsler IQ taking into consideration other parameters that may be of significance in this study as seizures frequency, age at onset of epilepsy and EEG abnormality. Data are collected and statistically analyzed using Mann Whitney test for correlation Statistic, Paired sample Statistic test for evaluation of Statistic differences.

Results

Job-shop By comparing the IQ of all the studied patients before and after treatment, it was ranged from 80-105 before treatment with a mean 91.65 ± 7.1 while it was ranged from 75 to 100 after treatment with a mean 88.75 ± 7.7 with significant difference ($P < 0.01$) (Table 1). Among them, patients whose IQs were < 90 before treatment, their mean IQs before treatment were 83.62 ± 3.12 while their mean IQs after treatment were 79.31 ± 3.57 , there is a significant (+ve) correlation between IQs before and after treatment in those patients whose IQs before treatment were < 90 (p -value < 0.01), While those patients whose IQs before treatment were ≥ 90 , their mean IQs before treatment were 95.52 ± 4.73 with a mean IQs after treatment 93.3 ± 4.16 with no significant difference.

Table 1: Comparison between IQ before and after treatment

	Before treatment	After treatment
Mean \pm SD	91.65 \pm 7.06	88.75 \pm 7.72
Range	80 – 105	75 – 100
P-value	0.000*	

Paired samples t-test

* Statistical significant difference ($P < 0.05$)

-Regarding the individual groups, there was a significant difference in each group between IQs before and after treatment. with no significant difference between the groups in the IQ values after treatment (Table

Table 2 : Before and after treatment IQs in different groups of the study.

	Group A Mean+ SD	Group B Mean+ SD	Group C Mean+ SD	Group D Mean+ SD
IQ before	92.5+85	91.3+5.8	91+7	91.8+7.6
IQ after	89.1+8.3	89.1+7.4	87.7+7.6	89.1+5.6
P-Value	<0.001	<0.01	<0.01	<0.01
significance	significant	significant	Significant	significant

-There is statistically significant (+ve) correlation between IQs after treatment and mothers' IQs and so like between patient after treatment and Father's IQs in the all studied groups(p- value<0.05)(Table 3&4).

Table 3: Correlation between IQs of Patients after treatment and mothers' IQs

	Group A Mean+ SD	Group B Mean+ SD	Group C Mean+ SD	Group D Mean+ SD
IQ of mothers	90.5+7.1	90+6.4	92+7.7	92.1+7.2
IQ after	89.1+8.3	89.1+7.4	87.7+7.6	89.1+5.6
P-Value	<0.05	<0.05	<0.002	<0.001
significance	significant	significant	Significant	significant

Table 4 : Correlation between IQs of Patients after treatment and fathers' IQs

	Group A Mean+ SD	Group B Mean+ SD	Group C Mean+ SD	Group D Mean+ SD
IQ of Fathers	92.5+2.5	93.5+8.6	89.8+6.7	92.5+8.5
IQ after	89.1+8.3	89.1+7.4	87.7+7.6	89.1+5.6
P-Value	<0.05	<0.05	<0.01	<0.001
significance	significant	significant	Significant	significant

-From the study we conclude that there is a statistically highly significant difference between IQs before and after treatment in patients whose EEG are irritative (p value = 0.000) which is more significant than that of those patients whose EEGs are normal (p value = 0.029)(Tab 5).

Table(5): IQ before and after treatment with the finding of the EEG.

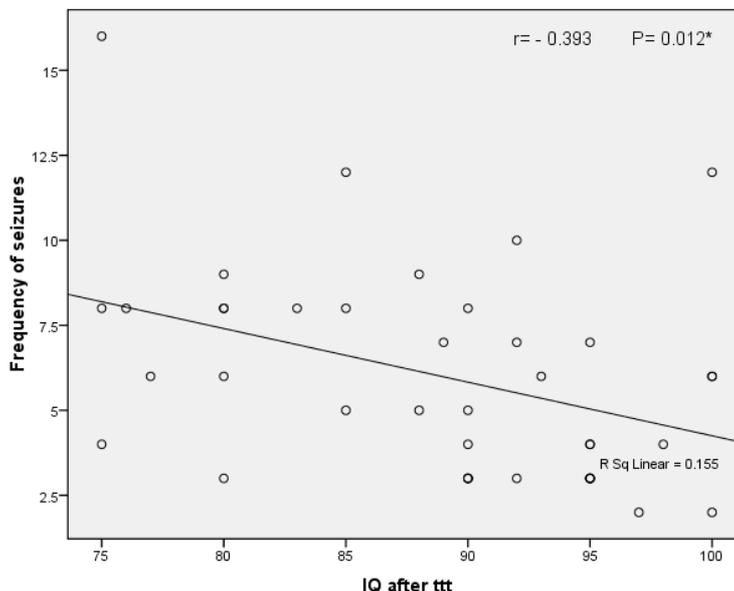
		Patients whose EEGs are irritative	Patients whose EEGs are normal	P-value
Before treatment	Mean ± SD	91.2 ± 7.8	92.7 ± 5.1	0.215
	Range	80 – 105	85 – 105	
After treatment	Mean ± SD	87.8 ± 8.4	91.1 ± 5.4	0.558
	Range	75 – 100	80 – 100	
P-value		0.000*	0.029*	

Paired samples t-test

* Statistical significant difference (P < 0.05)

-From the study we can conclude that there is statistically non significant (-ve) correlation between IQs after ttt and frequency of seizures (p- value >0.05) (Fig 1)

Fig. (1): Correlation between patients' IQs after treatment and frequency of seizures



-Regarding group A, whose EEGs were normal (20%) showed no difference in their mean IQs before and after treatment, while those whose EEGs were irritative (80%) showed difference in their mean IQs before and after treatment, also there is a statistically significant difference between IQs before and after treatment in those whose IQs before treatment were < 90 (p-value 0.02). Indicating that those patients whose IQs before treatment are lower, their parents' IQs tend to be low and their IQs are more liable to be affected after treatment. and vice versa i.e those patients whose IQs before treatment are higher, their parents' IQs tend to be high and their IQs are less liable to be affected after treatment. and this conclusion may support the role of heredity in cognitive affection after treatment with AEDs.

-Regarding group B, whose EEGs were normal (30%) showed mild difference in their mean IQs before and after treatment, while those whose EEGs were irritative (70%) showed marked difference in their mean IQs before and after treatment. Also there is a statistically highly significant (-ve) correlation between IQs after treatment and Seizure Frequency (p-value <0.01). Furthermore, we can find out that in those patients whose IQs before treatment were < 90 show statistically significant difference between their IQs before and after treatment, while those whose IQs before treatment were ≥ 90 , show statistically no significant difference between their IQs before and after treatment.

-Regarding group C, whose EEGs were normal (40%) showed some difference in their mean IQs before and after treatment, while those whose EEGs are irritative (60%) showed larger difference in their mean IQs before and after treatment. However, in group D there is statistically significant (+ve) correlation between IQs after treatment and frequency of seizures (p-value=0.006) (p-value <0.01)

Discussion

In our study we found that there is +ve correlation between the age at onset of seizures and the impairment in cognitive functions in epileptics i.e. the younger the patient at the onset of seizure, the lesser the decline in cognitive function, in partial disagreement with several studies done of Dodrill CB, et al, 1992 with Liu, et al, 2002 which emphasized that age of onset is, in fact, the most important predictor of cognitive outcome in patients with epilepsy. Regarding the effect of seizure frequency on cognitive functions in epileptic patients, the present study revealed that there is (-ve) correlation between seizure frequency and cognitive outcome in all patients and in group (B) i.e. the higher the frequency of seizure, the lower the cognitive outcome. This result comes in agreement with study of Tonekaboni, et al, 2006. however, and in disagreement with study done by Glória Maria, et al, 1999 who found that no relationship was found between the number of the attacks of benign Rolandic epilepsy with centro-temporal spikes (CTS) and the results in the WISC-III (Wechsler Intelligence Scale for Children—3rd copy).

In the present study, There is statistically highly significant difference between IQs before and after treatment in patients whose EEG are irritative ,which is more significant than that of those patients whose EEGs are normal ,this discrepancy between the two subgroups which may apparently attributed to EEG abnormalities , may be actually attributed to other factors as higher frequency of seizures . This results are in partial disagreement with study done by Pinton F. , et al , 2006 who found that no significant association was observed in their study between inferior performance in the WISC and the EEG abnormality. In the present study there is (+ve) correlation between IQ before and after treatment in the 4 groups i.e. IQ after ttt is in direct proportional to IQ before treatment, In other words, patients with lower IQ before treatment are more liable to decline of their IQs after treatment with the AEDs and this reflect the effect of the hereditary factor as a major counterpart that affect cognitive function . IQs of patients after treatment is in statistically significant (+ve) correlation with that of their parents. and with patient's IQs before treatment Which in turn may reflect , to a great extent, the role of heredity as an important factor in cognitive change after usage of AEDs. This conclusion comes in agreement with Deckers, et al, 2000.

The difference in cognitive functions seen in group A and B which may be attributed ,in partial to ,CBZ and VPA respectively comes in agreement with Dodrill , 2000 who in their study found that both CBZ and VPA have similar cognitive effects which are typically mild in magnitude. And in partial disagreement with Cavanna 2010 who mentioned that, the active metabolite CBZ-epoxide is partly responsible for the mild cognitive and psychomotor effects attributed to CBZ. Also in partial disagreement with Lee et al., 2006 and Mula,et al ,2006 who also mentioned that CBZ may cause irritability, impaired attention and behavioral problems in patients with existing behavioral difficulties.

The difference in cognitive functions seen in group C and D which may be attributed ,in partial to ,LTG and TPM respectively . It comes in agreement with Meador, et al , 2005 who found that in two large studies LTG has fewer central effects than CBZ or PHT ,also in agreement with Pavel , et al , 2004 who found that topiramate had more deleterious effect on cognition than LTG and VPA in study don on volunteers. in partial disagreement with Jokeit and Ebner, 2002 who found that LTG has a favorable cognitive and behavioral profile in epilepsy patients and in partial disagreement with Mula et al., 2006 Who added LTG diminishes depression and mania and has mood stabilizing effect as well as improves energy and social function . As regard group D the result of our study come in agreement with the study of Martin, et al ; 1999 who found, in a study on volunteers, that TPM produce significantly greater effect on cognitive function than LTG and GBP. and in disagreement with Loring, 2007 who found in a comparative study between TPM and VPA when added to CBZ. And after analysis of individual data .that scores were generally unchanged or even improved after TPM and VPA. This means that there is a subset of Patients Who are particularly susceptible to the cognitive side effects of TPM. in disagreement with Sloviter et al., 2003 who mentioned that Cognitive and behavioral problems associated with TPM use are of significant concern in patients with epilepsy and in disagreement with Caplan, et al, 2008 who mentioned that both cognitive and behavioral problems with TPM are less frequent and severe when the starting dose is low and increased slowly. Our study demonstrated that , the main factor responsible for the cognitive decline with the use of the AEDs is the heredity , come in agreement with Desai, 2008 who mentioned that heredity had a major role in cognitive affection in addition to other factors as epilepsy itself , medications and brain injuries already present. and In partial agreement with Blake ,et al, 2000 who mentioned that AEDs can positively improve mood and behaviour through anti-seizures mechanisms or release phenomenon (i.e. successful seizure control with AED is associated with a positive impact on alertness and cognition) and in partial agreement with Seo, et al, 2007 who mentioned that it is currently not possible to predict which patient with epilepsy will tolerate an AED or develop positive or negative psychotropic effects. As regard the -ve effect of seizure frequency on cognitive functions, that our study demonstrated that seizure frequency had -ve effect on cognitive functions and this result come in agreement with Aldenkamp and Arends 2005 who concluded that within a population of patients with all kinds of seizures, those with more than 100 secondary generalized seizures perform less well on tests for intellectual and cognitive functioning, including memory as well as long-time accumulation of intellectual deterioration due to multiple seizures. As regard the EEG , our study revealed that EEG abnormality had -ve effect on cognition which come in agreement with Meador, 2002,who mentioned that the localization of the epileptic focus is also an important determinant of the extent and nature of cognitive deficits and in partial agreement with Bergin et al, 2000. Patients with TLE are reported to have more memory impairments than patients with extra-temporal epilepsies and both groups have more memory impairments than patients with generalized epilepsies and in agreement with Helmstaedter et al, 2001 who mentioned that Frontal lobe epilepsy is often associated with performance deficits in executive functioning In addition, foci in the left

temporal lobe are related to verbal memory impairments. Also, in agreement with Kaufman et al, 1997 and Blake et al, 2000.

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