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Clinical Science

Monotherapy versus Polytherapy in Epileptic Adolescents

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Abstract

Objective: Comparison between the effect of monotherapy and polytherapy on cognitive functions and growth measurements among epileptic adolescents.

Methods: This study was carried on 57 adolescents from those with antiepileptics either monotherapy or polytherapy, in comparison with 20 controls. All were exposed to full neurological examination, Psychometric studies using Revised Behavior Problem Checklist "RBPC", anthropometric measurements including height, weight, estimation of blood haemoglobin "Hb", serum levels of copper and zinc.

Results: We found that 29 cases were with monotherapy and 28 cases were with polytherapy. Scores of RBPC revealed that conduct disorders, socialized aggression and social anxiety withdrawn scales, showed significant increase in epileptic adolescents in comparison with controls which is more in cases with polytherapy, with higher frequency in distractability and restlessness in those with monotherapy. Those with polytherapy showed high frequency in depression and psychomotor retardation. Levels of heamoglobin, copper, and zinc was statistically decreased among epileptics, more with Polytherapy. There was increase in weight and BMI with monotherapy while there was decrease in weight and BMI with polytherpy as compared with controls.

Conclusion: Epileptic patients with monotherapy scored better cognitive functions, than those with polytherapy. So we recommend monotherapy in treatment of epilepsy for better cognitive functions.

Introduction

About 50 million people worldwide have epilepsy, and nearly 90% of epilepsy occurs in developing countries [1]. Epilepsy becomes more common as people age [2, 3]. Epilepsy is one of the most common of the serious neurological disorders [4]. About 3% of people will be diagnosed with epilepsy at some time in their lives [5]. The prevalence of active epilepsy is roughly in the range 5–10 per 1000 people. Epilepsy's approximate annual incidence rate is 40–70 per 100,000 in industrialized countries and 100–190 per 100,000 in resource-poor countries; socio economically deprived people are at higher risk. In industrialized countries the incidence rate decreased in children but increased among the elderly during the three decades prior to 2003, for reasons not fully understood [6].

Epilepsy is usually controlled, but not cured, with medication. However, over 30% of people with epilepsy do not have seizure control even with the best available medications. Surgery may be considered in difficult cases [7, 8].

During adolescence and adulthood, the causes are more likely to be secondary to any CNS lesion. Further, idiopathic epilepsy is less common. Other causes associated with these age groups are stress, trauma, CNS infections, brain tumors and illicit drug use and alcohol withdrawal [9].

The mainstay of treatment of epilepsy is anticonvulsant medications. Often, anticonvulsant medication treatment will be lifelong and can have major effects on quality of life. Mechanisms, effectiveness for particular epilepsy syndromes, and side-effects differ among the individual anticonvulsant medications. Some general findings about the use of anticonvulsants include availability, effectiveness, safety and side effects. The goal for individual patients is no seizures and minimal side-effects, and the job of

the physician is to aid the patient to find the best balance between the two during the prescribing of anticonvulsants. Most patients can achieve this balance best with monotherapy. Some patients, however, require polypharmacy, the use of two or more anticonvulsants.

Monotherapy has been promoted as the ideal in epilepsy treatment because of reduced side effects, absence of drug interactions, better compliance, lower cost and, in many cases, improved seizure control compared to polytherapy. The question of monotherapy vs. polytherapy has assumed increasing importance with the availability of multiple **new** antiepileptic drugs (AEDs). However, a high percentage of patients with resistant epilepsy are treated with polytherapy, which probably benefits only a minority of them. The availability of multiple drugs with different mechanisms of action favours the possibility of "rational polytherapy", taking advantage of possible synergism, a yet unproven concept. Initial AED monotherapy is effective in rendering approximately 60% of epilepsy patients' seizure free [10].

It was found that 40% of patients failing phenytoin or carbamazepine monotherapy respond to polytherapy, with 11% of these patients becoming seizure-free [11]. The American Academy of Neurology/ American Epilepsy Society (AAN/AES) Practice Guidelines for the treatment of refractory epilepsy supports the use of second-generation AEDs for adjunctive treatment of refractory partial-onset seizures in adults [12].

This study aimed to evaluate the effect of antiepileptic monotherapy and polytherapy on cognitive functions and growth measurements among epileptic adolescents.

Material and Methods

This study was carried on 57 epileptic adolescents of both sexes (30 males and 27 females) their ages ranged between 14 up to 18 years old from those attending the outpatient clinic of Neurology in Red Cresent Hospital “Suzan Mubarak Hospital, Giza, Egypt,” over a period of two years from April 2008 till May 2010. Twenty healthy non epileptic adolescents of matched age and sex with no history of organic and neurological diseases were included to serve as controls, they were selected among those living under more or less the same socioeconomic standards as those included in our study, selected from the relatives of the patients.

Cases were classified into two groups, those who were with monotherapy (Group I = 29 cases), and those who were with polytherapy (Group II = 28 cases), the last group include the controls (Group III = 20 normal adolescents). Informed consent was signed by the parents of the children and controls to participate in the study including the following:

- Full general and neurological assessment, including full history and examination according to sheet prepared for the study.

- Psychometric studies using Revised Behavior Problem Checklist (RBPC) [13] translated in Arabic [14].

- Measure general cognitive abilities using the Wechsler Intelligence Scale “WISC” for children/adolescents, it provides information about general IQ (or 'intelligence') as well as areas of intellectual strength and difficulty. The WISC is comprised of four main areas:

- Verbal Comprehension (verbal abilities);
- Perceptual Reasoning (non-verbal abilities);
- Working Memory (verbal working memory);
- Processing Speed (visuo-motor speed).

- Anthropometric measurements including height, weight and calculation of weight for age and height for age [15, 16].

- Laboratory studies: Three milliliters of fasting venous blood were drawn with a sterile plastic syringe from each case and control. One milliliter of the blood was gently placed in a dry clean plastic tube containing EDTA as a blood anticoagulant for the estimation of blood Hb concentration, using cyanomethe-hemoglobin method according to the procedure described by Betke and Savelsberg [17] using Drabkin’s solution as a diluent. The rest 2 ml blood were gently placed in a dry clean plastic tube and left for 15 minutes to clot then centrifuged at 3500 rpm for separation of serum, which then kept in deep freeze at -70ºC until analysis for estimation of serum levels of, copper and zinc.

- Statistical analysis: All data obtained were statistically analyzed using Microsoft Excel and SPSS 11.5 for windows software package including, “t test, non parametric Qui square, Mann Whitney and Anova test”.

Results

Scores of RBPC revealed that conduct disorders according to DSM-IV Diagnostic Criteria for Conduct Disorder, showed a statistically significant increase in epileptic adolescents in comparison with controls which is more in cases with poltherapy. Socialized aggression and social anxiety withdrawn scales show significant increase in epileptic adolescents in comparison with controls which is more in cases with polytherapy.Scores of attention problems and motor excess scales and psychotic behavior changes show no statistically significant differences between groups (Table 1).

Table 1: Revised Behavior Problem checklist in epileptic patients and controls.

Groups	CD	SA	AP	AW	PB	ME

Group (III) Controls						
Mean	8.64	1.13	4.27	5.23	0.05	3.96
±SE	3.15	0.36	1.43	1.45	0.01	1.76
Group (I) Epileptic Adolescents under Monotherapy						
Mean	13.58	1.4	18.6	5.7	0.88	5.83
±SE	3.04	0.25	3.07	2.03	0.09	1.02
P1	0.001	0.1	0.001	0.2	0.03	0.003
Group (II) Epileptic Adolescents under PolytherapyM						
ean	19.93	3.7	15.67	8.65	0.73	0.86
±SE	4.72	1.05	2.8	2.76	0.07	0.45
P2	0.001	0.001	0.001	0.001	0.05	0.001
P3	0.002	0.02	0.03	0.001	0.2	0.001

P1: Epileptic adolescents receiving monotherapy Vs Controls; CD: Conduct Disorders; P2: Epileptic Adolescents receiving Polytherapy Vs Controls; SA: Socialized Aggression; P3: Epileptic Adolescents receiving Monothrapy Vs Polytherapy; AP: Attention Problems; P >0.05 non significant; P< 0.05 Significant; AW: Anxiety &Withdrawal; P< 0.01 Highly Significant; P < 0.001 Very high significant; PB: Psychiatric behavior ME; motor excess.

There was a statistical significant difference between group I and Group II with higher frequency in distractability and restlessness in adolescents with monotherapy, while high frequency in depression and psychomotor retardation were statistically significant in adolescents with polytherapy (Table 2).

Table 2: Psychiatric Changes among Epileptic adolescents in the study.

Psychiatric Manifestations	X2	P
Behavioral Problems:		
Aggression	0.3	>0.05
Restlessness	1.02	<0.01
Retardation	3.2	<0.05
Mood Disorders:		
Depression	29	<0.05
Cognitive Disorders:		
Lack Of Concentration	1.5	>0.05
Distractability	2.8	<0.05
Speech Disorders	0.4	>0.05

P > 0.05 non significant; P < 0.05 Significant; P < 0.01 Highly Significant; P < 0.001 Very high significant .

There was a statistical significant decrease in levels of heamoglobin, copper, and zinc between epileptic adolescents and controls which is more in group II “Polytherapy” than Group I “Monotherapy” (Table 3).

Table 3: Mean Values of Hemoglobin, serum copper and Zinc in Epileptic Adolescents and controls.

Groups	Hb (g/dl)	Copper µg/dl	Zinc µg/dl
Group (III) Control			
Range	12.3 – 13.7	81 – 159	75 – 137
Mean	12.6	110.4	103.8
± SE	0.24	4.8	4.76
Group (I) Monotherapy			
Range	10.2 – 11.6	79 – 155	73 – 130
Mean	10.9	104.7	99.2
± SE	0.68	6.4	2.5
P	0.001***	0.01*	0.05*
Group (II) Polytherapy			
Range	9.61 – 11	75 – 149	70 – 120
Mean	9.95	100.5	92.3
± SE	0.23	3.9	2.04
P	0.001***	0.002**	0.005**

P >0.05 non significant; P< 0.05 Significant; P < 0.01 Highly Significant; P < 0.001 Very high significant .

Anthropometric measurements in our study included weight and height measurements with weight for age and height for age. There was a highly significant increase in weight for age in adolescents with monotherapy while there was a significant decrease in the weight for age in adolescents with polytherapy as compared with controls (Table 4).

Table 4: Weight for age and height for age among epileptic adolescents and controls.

Groups	Height for age	Weight for age
Group (III) Control		
Range	159 - 170	49 – 64
Mean	164.3	57.5
± SE	3.7	2.33
Group (I) Monotherapy		
Range	158 – 168	53 – 73
Mean	160.6	66.3
± SE	1.45	3.4
P	0.06	0.002***
Group (II) Polytherapy		
Range	159 – 167	50 – 64
Mean	161.2	53.25
± SE	0.76	2.15
P	0.13	0.01*

P > 0.05 non significant; P< 0.05 Significant; P < 0.01 Highly Significant; P < 0.001 Very high significant.

Discussion

In this study, distribution of drug intake among epileptic patients study showed that 29 cases with monotherapy, of them 16 cases are using valproic acid, 10 cases are using carbamazepine, and only 3 cases are using phenytoin treatment. For cases with polytherapy there were 28 cases receiving valproic acid with other antiepileptic drugs (6 cases with phenytoin and 12 cases with carbamazepine and 4 cases with topamax).

According to Mula and Trimble 2009, cognitive dysfunction is frequently observed in patients with epilepsy and represents an important challenge in the management of patients with this disorder. Drug treatment requires careful balancing in the attempt to reach maximal seizure control while avoiding neurotoxic adverse effects [18], and this is agreed with results of our study as we found that there are cognitive disorders among both groups in comparison with controls. In our study there is no significant difference in the occurrence of epilepsy, growth retardation and cognitive functions according to their sex, which means that males and females are equally affected, these results were agreed with studies done by Devinsky et al., 1995 and Kocken 1997 [19, 20], who reported that epilepsy stigmatize both sexes equally. While McGuire 1991 [21], noticed a minimal difference between males and females with epilepsy regarding their psychological aspects as anxiety and depression and their social activities.

We found that there was a significant increase in conduct disorders, socialized aggression as well as anxiety withdrawn scales in epileptic adolescents under polytherapy as compared with group under monotherapy and controls. These results were agreed with Mattson et al., 1985 [22], who reported that there was more difficulties in cognitive functions with phenytoin as compared with carbamazepine in partial and secondary generalized seizures. Regarding the

psychotic behavior problems there was no significant differences between the three groups, in agreement with studies done by Sabers et al. 1995 [23] and Craig and Tallis 1994 [24] who found no differences between antiepileptic drugs as regards their effect on cognitive functions in epileptic adolescents.

In this study we found that adolescents receiving monotherapy had higher scores regarding the cognitive function scale as compared with those under polytherapy and this was simulate the study done by Gillham et al. 1996 [25], and supported by study done by Reynolds and Shorvon 1981 [26], who reported that although anticonvulsant polytherapy has been widely and traditionally used in the treatment of epilepsy, there is little evidence of its advantages over monotherapy. It does, however, lead to problems of chronic toxicity, drug interactions, failure to evaluate individual drugs, and sometimes exacerbation of seizures. Also Erik and St. Louis in 2009 [27] reported that Monotherapy is usually preferred over polytherapy whenever possible in epilepsy care. However, a substantial number of patients with intractable epilepsy may respond to AED polytherapy. Appropriate uses of more than one AED include transitional polytherapy during conversion to a new monotherapy, and chronic maintenance polytherapy in refractory patients. When a patient becomes seizure-free while receiving polytherapy, it may be possible to taper and gradually discontinue the baseline AED which has been previously ineffective or poorly tolerated.

It was concluded that adolescent epileptic patients under monotherapy with AEDs scored better regarding their cognitive functions as well as their physical development than those under polytherapy with AEDs. So it is better to use only one AED for treatment of epilepsy for better cognitive functions

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