The Impact of Antiepileptic drugs on Cognitive and Behavioral Functions in chlidern with Idiopathic Generalized Epilepsy

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Abstract:

Epilepsy was documented as a neurological disorder, but nowadays, there are accumulating evidences that it is a behavioral – cognitive disorder as well. ***Subjects:*** This study was conducted on 60 freshly diagnosed epileptic children (43 boys and 17 girls) suffering from idiopathic generalized tonic – clinic seizures to evaluate the effects of AED's on their cognitive functions and behavior. The mean age at presentation was 10 ± 4 y (range 6 to 14yr). All children were attendants of Pediatric Neurology Inpatient wards and Outpatient Clinic of Pediatric Department, Tanta University Hospital. Diagnosis of epilepsy was based on clinic grounds. EEG recordings, plain X-ray skull and brain C.T. scanning. 15 Healthy children, products of nonepileptic families and of matched age and sex served as controls. Patients were classified randomly into 4 subgroups according to AED used as follows: PHT – treated subgroup (15 cases). PB – treated subgroup (15 cases) . CBZ – treated subgroup (15 cases) . VPA – treated subgroup (15 cases). ***Methods:*** The following investigations were done for all children before and 6 months after the start of AED therapy: I- Image studies as x-ray skull, C.T. brain. & EEG. II- Estimation of serum level of AED's by high – pressure liquid & gas chromatography. III- Quick Neurological Screening Test (QNST). IV- Cognitive function tests: Wechsler Intelligence Scale for Children – Revised (WISC-R). Hiskey – Nebraska Scale for Learning Aptitude (HN.S). V- Adjustment Scale for children (ASC) VI- Total school academic score (TSAS).

- ***Results :*** The present work demonstrated that children suffering idiopathic generalized tonic – clonic seizures, before initiation of AED therapy and cognitive and behavioral disturbances as evidenced by lower results of the various test utilized. This behavioral and cognitive impairment became worse after PHT & PB monotherapy inspite of

seizure control, while the behavioral & cognitive functioning got better after CBZ & VPA monotherapy. PHT was more damaging on cognition while PB was more damaging on behavior. The impaired cognitive and behavioral functions before treatment can be explained by the psycho-social perception of epilepsy in homes and schools of epileptic children and ictal and inter-ictal epileptiform activity with their cognitive and behavioral impacts on the maturing brain. The deterioration of cognitive functions and behavior caused by PHT & PB may be explained by their reducing effects on the local cerebral blood oxygen and glucose metabolism and reduction of acetylcholine esterase activity. The positive effects of CBZ and VPA on cognitive functions and behavior could be explained by the structural resemblance of CBZ to tricyclic antidepressants, with stabilizing effect of both drugs on the limbic system, anti – kindling effects and reduction of both glutamate release and dopamine – nor adrenaline turnover are also possible mechanisms.

Conclusions

1. Epilepsy in children is not only a neurological problem but a behavioral – cognitive one as well. 2. AED's significantly modify cognitive functions and behavior in epileptic children. 3. PHT & PB have deleterious effects on cognition & behavior PHT is more damaging on cognition while PB is more damaging on behavior. 4. CBZ & VPA have positive effects on cognition & behavior. 5. This work proved the validity of "Kamel's Holistic Model of Brain function" as an explanation of integration of brain centers in the various processes of thinking, cognition and behavior. 6. The degree of affection of certain AED on this aspect depends on its booting or de-booting effect on anterior and posterior learning processors.

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Introduction

Epilepsy is defined as recurrent seizures unrelated to fever or to an acute cerebral insult. Generalized epilepsy is diagnosed when no evidence of localized onset could be found and it is characterized as idiopathic when its causes can not be ascertained.(1)

The primary aim of the treatment of epilepsy is the complete control of seizures without the precipitation of appreciable side effects of anti-epileptic drugs (AED'S).(2)

There are accumulating evidences that AED therapy can badly affect the cognitive and behavioral functions specially in children who have fragile & rapidly developing brains.(3)

Many authors and research institutes contributed in this issue as Mcleod et al(4) who stated that phenobarbital impair memory and concentration.

Also, Gallassi et al (5) recorded that phenytoin affects attention, problem solving and visumotor tasks( ).

Dodson stated that carbamazepine has good effects on attention span and motor steadiness.(6) D'oughtery and Wright(7) reported similar advantages at lower doses but deleterious effects on high doses.

Vining et al [8] reported that valproate would appear to have minimal effects on cognition. Therefore, it appeared both useful and interesting to study any possible effects of a given AED on the various aspects of cognitive and behavioral functions in children on therapy.[9]

Aim of the work

1- This research aimed to study the effects of anti-convulsant therapy on cognitive and behavioral tasks in children suffering epilepsy.

2- The study aims at testing a hypothesis about the formation of functional learning processors: anterior learning processors (ALP) and posterior learning processors (PLP) in cerebral cortex who are responsible for cognitive and behavioural functions (Kamel A.M, 1993).

It is supposed that epilepy make disturbance in these functional units in cortical and subcortical formations so it has bad and negative effect upon cognitive and behavioural finctions.

3- Booting hypothesis

The brain as a holistic system works integratively, then all cortical and subcortical centers have the posibility for getting in mutual sense. Sensing process between centers is achieved by learing and sensory education. (conditioning operation conditioning modeling, trial and error). The process by which brain centers sense each other is called booting mechanism (Kamel. A.M, 1999, P. 412.413).[34]

This mechanism is considered to be very essential in all cognitive, emotional and psychomotor functions of the brain.

The cognitive functions of the brain includes: attention,

perception, visual closure, memory (verbal, colour, digits), thinking (comparison, analysis, synthesis processes) problem solving. These function and others occur by learning processors: A.L. P.&P.L.P. (Kamal A.M, 1993) in cerebral cortex and which can be measured with objective scales: Wechsler intelligence scale for children WISC, Hisky-Nebraska, child behavior rating scale (CBRS) &quick neurological screening test (QNST).

Epilepsy causes disharmony not only between cerebral centers but also inside the learning processors (Kamal A.M 1993).[44]

N.B.: A.L.P: frontal, central and temporal zones and P.I. P: temporal, occipital, parietal zones. Authors suppose that some AED may restore or support Booting mechanism so it keep and improve cognitive and behavioral functions beside good control upon convulsions but others not.

Cases selection

This work was carried out on 60 children aged 6-12 years freshly diagnosed as having idiopathic generalized epilepsy. They were admitted at neurology unit of pediatric department, Tanta university Hospitals.

They were classified into 4 groups according to medication given as follow.

1- 15 patients received Phenobarbital monotherapy.
2- 15 patients received Phenytoin monotherapy.
3- 15 patients received Carbamazepine monotherapy.
4- 15 patients received valproate monotherapy.

Another 15 healthy children with matched age and sex served as controls.

Exclusion Criteria

The child is excluded in case of having any of the following signs 1-IQ, (WISC) LESS THAN 90, 2-any

neurological impairment other than epilepsy 3-interrupted course or pervious anti-convulsant drug. 4-EEG abnormality shows focal lesion, isolated single seizures 6-Hemoglobin less than 9 gm%. 7-impairment of liver or kidney functions.

Tools & Methods

The methodology of this work was based on the "inter-disciplinary approach" which depends on the contribution of both medicine and psychology.

All children were subjected to the following:

(i) Full history taking with thorough clinical and neurological examination.

(ii) Routine laboratory investigations as:
   1. Complete blood picture.
   2. Liver function tests.
   3. Kidney function tests.

(iii) Investigations to diagnose idiopathic generalized epilepsy.
   1. Plain X-ray skull.
   2. Brain computed axial tomography scanning (CAT scan).
   3. Electroencephalography (EEG).

(iv) Suitable Battery of several psychometric scales for study of main aspects of cognitive functions such as memory, attention span, concentration, thinking visual closure....etc
   1. Wechsler Intelligence Scale for Children (revised) (WISC-R)[10]
   2. Hisky-Nebraska Scale[11]

(v) Evaluation of child behavior using CBRS, which

measure, children adjustment as home, self, social, physical [12] adjustments.

Quick Neurological screening test F. Estimation of serum level of AED by chromatographic methods. [14]

Patients were studied at admission and 6 months later of initiation of AED monotherapy.

Statistical analysis

1) Descriptive statistics.
2) One-way ANOVA
3) Sheffe-test.
4) Computing by SPSS program

Results

Table (1) Quick Neurological Screening test before & after AED therapy

	Controls	Total cases (n=60) before ttt	Phenytoin PHT (n=15)		Phenobarbitone PB. (n=15)		Carbamazepine CBZ. (n=15)		Valproic Acid (n=15)	
			Before ttt	After ttt	Before ttt	After ttt	Before ttt	After Ttt	Before ttt	After ttt
Mean	8.9	10.8	10.2	18.1	10.4	15.1	11.3	8.7	11.3	9.1
S.D.	4.3	3.2	2.6	3.1	3.3	4.1	3.1	2.9	4.2	9.2
P1	NS									
P2				* ↑		* ↑		NS		NS
P3				* ↑		* ↑		* ↓		* ↑
ANOVA by. scheffe t.	P4 * ↑	P5 * ↑		P6 * ↑		P7 * ↑		P8 * ↑		P9 NS

P1: Total cases before ttt *Vs.* controls
P2: Patient group after ttt *Vs.* controls
P3: Patient group before ttt *Vs.* after ttt
P4: PHT *Vs.* PB P5: PHT *Vs.* CBZ
P6: PHT *Vs.* VPA P7: PB *Vs.* CBZ
P8: PB *Vs.* TPA P9: CBZ *Vs.* VPA
* P significant < 0.05 N.S. = non significant

Table (1) shows the quick neurological screening test in controls and patients groups before and after AED therapy

- It shows insignificant increase of the score of QNST in

epileptic children before initiation of AED as compared to controls denoting minimal derangement of their gross and fine motor neuro-developmental function.

- PHT & PB treatment resulted in further significant increase of the score denoting more neurodevelopmental motor derangement.
- CBZ & VPA treatment resulted in significant decrease of the score to a mean level insignificantly different from control group denoting partial improvement of the neuro-developmental disruption.
- PHT treated group showed significantly higher score than PB, CBZ & VPA treated groups.
- PB treated group showed significantly higher score than CBZ & VPA treated groups.
- CBZ treated group showed significantly lower score than VPA treated group.

Table (2) H.N. scale performance tasks before & after AED therapy

	Controls (n=15)	Total cases (n=60) before ttt	Phenytoin PHT (n=15)		Phenobarbitone PB. (n=15)		Carbamazepine CBZ. (n=15)		Valproic Acid (n=15)	
			Before ttt	After ttt	Before ttt	After Ttt	Before ttt	After Ttt	Before ttt	After ttt
Mean	105.7	105.5	105	81.9	89.9	109.9	123.3	103.3	103.6	104.5
S.D.	10.3	16.1	12.3	12.4	6.7	9.7	12.1	9.9	24.5	22.5
P1	NS									
P2				* ↓		* ↓		* ↑		NS
P3				* ↓		* ↓		* ↑		NS
ANOVA by scheffe t.	P4 * NS	P5 * ↓		P6 * ↓		P7 * ↓		P8 * ↓		P9 ↑

* Learning quotient L.Q.

P1: Total cases before ttt *Vs.* controls

P2: Patient group after ttt *Vs.* controls

P3: Patient group before ttt *Vs.* after ttt

P4: PHT *Vs.* PB P5: PHT *Vs.* CBZ

P6: PHT *Vs.* VPA P7: PB *Vs.* CBZ

P8: PB *Vs.* TPA P9: CBZ *Vs.* VPA

* P significant < 0.05 N.S. = non significant

*** Peformance test score (HN.S):**

- Epileptic children before initiation of AED therapy had HN.S insignificantly different from that of controls.
- PHT & PB treatment resulted in significant decrease of the HN.S to levels significantly lower than that of controls.
- CBZ treatment resulted in significant increase of the HN.S to a level significantly higher than that of controls.
- VPA treatment resulted in non-significant change of the HN.S.
- PHT treated group showed significantly lower HN.S than CBZ & VPA treated groups.
- PB treated group showed significantly lower HN.S than CBZ & VPA treated groups.
- CBZ treated group showed significantly higher HN.S than VPA treated group.

Table [3] WISC-R-Performance tasks before & after AED therapy

	Controls (n = 15)	Total cases (n=60) before ttt	Phenytoin PHT. (n=15)		Phenobarbital PB. (n=15)		Carbamazepine CBZ. (n=15)		Valproic Acid (n=15)	
			Before ttt	After ttt	Before ttt	After Ttt	Before ttt	After ttt	Before ttt	After ttt
Mean	102.6	107.0	106.5	83.2	106.6	86.7	102.9	104.3	105.6	102.6
S.D.	13.2	10.2	9.3	8.3	1.5	7.3	7.4	7.4	8.6	8.5
P1	NS									
P2				* ↓		* ↓		NS		NS
P3				* ↓		* ↓		NS		NS
ANOVA by scheffe t.	P4 * NS	P5 * ↓		P6 * ↓		P7 * ↓		P8 * ↓		P9 NS

P1: Total cases before ttt *Vs.* controls
P2: Patient group after ttt *Vs.* controls
P3: Patient group before ttt *Vs.* after ttt
P4: PHT *Vs.* PB P5: PHT *Vs.* CBZ
P6: PHT *Vs.* VPA P7: PB *Vs.* CBZ
P8: PB *Vs.* TPA P9: CBZ *Vs.* VPA
* P significant < 0.05 N.S. = non significant

Performance on non verbal subtest

- Epileptic children before initiation of AED therapy had quotients insignificantly lower than that of controls.

- PHT & PB treatment resulted in significant decrease of the performance subtest scores to levels significantly lower than that of controls.
- CBZ & VPA treatment resulted in insignificant difference from that of controls.
- PHT treated group showed significantly lower score than that of CBZ & VPA treated groups.
- PB treated group showed significantly lower score than CBZ, VPA treated groups.

Table (4) WISC-R- tasks before & after AED therapy Total intelligence quotient (I.Q)

	Controls (n = 15)	Total cases (n=60) before ttt	Phenytoin PHT (n=15)		Phenobarb PB. (n=15)		Carbamaz CBZ. (n=15)		Valproic Acid (n=15)	
			Before ttt	After ttt	Before Ttt	After Ttt	Before ttt	After Ttt	Before ttt	After tn
Mean	104.7	105.3	104.0	82.0	106.5	85.6	104.9	106.2	106.1	112.5
S.D.	14.5	8.2	24.9	9.0	10.3	8.9	12.9	7.7	9.2	9.2
P1	NS									
P2				• ↓		• ↓		NS		NS
P3				• ↓		• ↓		NS		NS
ANOVA by scheffe t.	P4 • NS	P5 • ↓	P6 • ↓		P7 • ↓		P8 • ↓		P9 NS	

P1: Total cases before ttt *Vs.* controls
P2: Patient group after ttt *Vs.* controls
P3: Patient group before ttt *Vs.* after ttt
P4: PHT *Vs.* PB P5: PHT *Vs.* CBZ
P6: PHT *Vs.* VPA P7: PB *Vs.* CBZ
P8: PB *Vs.* TPA P9: CBZ *Vs.* VPA
* P significant < 0,05 N.S. = non significant

Table (4) shows WISC – R, performance tasks before and after AED therapy

- Epileptic children before initiation of AED therapy had total intelligence quotients insignificantly different from that of controls.
- PHT & PB treatment resulted in significant decrease of the quotients to levels significantly lower than that of controls.

- PHT treated group showed significant lower quotients than CBZ & VPA treated groups.
- PB treated group shoed significant lower quotients than CBZ & VPA treated groups.

Table (5) Adjustment scale for children before & after AED therapy total adjustment

	Controls (n = 15)	Total cases (n=60) before ttt	Phenytoin PHT (n=15)		Phenobarbitone PB. (n=15)		Carbamazepine CBZ. (n=15)		Valproic Acid. (n=15)	
			Before ttt	After ttt	Before Ttt	After Ttt	Before ttt	After Ttt	Before ttt	After ttt
Mean	346	366	347	265	348	321	355	395	414	422
S.D.	61.3	51	130	77	99	88	42	23	42	57
P1	NS									
P2				* ↓		NS		* ↑		* ↑
P3				* ↓		* ↓		* ↑		NS
ANOVA by scheffe t.	P4 * NS	P5 * ↓		P6 * ↓		P7 * ↓		P8 * ↓		P9 * ↓

P1: Total cases before ttt *Vs.* controls
P2: Patient group after ttt *Vs.* controls
P3: Patient group before ttt *Vs.* after ttt
P4: PHT *Vs.* PB P5: PHT *Vs.* CBZ
P6: PHT *Vs.* VPA P7: PB *Vs.* CBZ.
P8: PB *Vs.* VPA P9: CBZ *Vs.* VPA
* P significant < 0.05 N.S. = non significant

Total adjustment

- Epileptic children before initiation of AED therapy had scores insignificantly different from that of controls.
- PHT treatment resulted in a significant decrease of the score to a level significantly lower than that of controls.
- PB treatment resulted in a significant decrease of the score to a level insignificantly different from that of controls.
- CBZ treatment resulted in a significant increase of the score to a level significantly higher than that of controls.
- VPA treatment resulted in an insignificant increase of the score to a level significantly higher than that of controls.
- PB treated group showed significantly lower score than CBZ & VAP treated groups.

- CBZ treated group showed significantly lower score than VPA treated groups.

Table (6) correlations coefficient between serum drug level (SDL) and psychometric measures*

Drug	QNST	HN S	WVES	WPRS	WTOS	TSAS	TADS
Phenobabital	+ 0.86	- 0.61	- 0 70	- 0 70	- 0.73	- 0.41	- 0.81
Phenytoin	+ 0.60	- 0.51	- 0.88	- 0.87	- 0.85	- 0.63	- 0.85
Carbamazepin	- 0.77	+ 0.72	+ 0.86	0.89	0.88	0.86	+ 0.74
Valproate	- 0.21	+ 0 52	+ 0.81	+ 0.81	+ 0 67	+ 0.84	+ 0.84

* WVES: verbal wisc, WPRS: performance wisc TADS: total Adustment score.

Table (6) shows that there are significant correlation between serum drug levels and different psychometric measures. The results clarify the impact of AED upon cognitive and behavioral functions. Carbamazepine, and valproate are the most safe drugs for maintaining cognitive and behovioural functions in addition to the complete control of seizures.

According to Kamel's Holistic model (1993, 1999) about Brain functions, valproate is the best drug helping in enhancement bootir ; mechanism among cortical and subcortical centers participating in all cognitive and behavioural functions. (Kamal A.M., 1999).

Behavioral functions before initiation of AED therapy

The present study demonstrated that children with idiopathic generalized tonic-clonic epilepsy suffered significant impairment of behavioural functions as tested by the behavioral observations sheet of adjustment scale for children (ASC modified from CBRS). These impairments were directly related to the duration of illness and to the frequency of fits before initiation of AED medication.

Weber et al., (1997) studied the behavioral characteristics of children with new-onset grand mal seizures. They found that 26% had clinically significant internalizing behaviors as anxiety and depression, while 37% had clinically significant externalizing behaviors as inattention and disruptive behaviors.[19]

Comparable findings reported by Dunn et al (1997) who

studied the behavioral problems in 18 children (aged 4-15 years) suffering new – onset idiopathic generalized tonic-clonic epilepsy. The parents rated their children's behavior on the child behavior checklist. They reported that 24% had already behavioral problems immediately prior to the first grand mal seizure. (20)

Austin et al (1997) studied 88 epileptic children and their mothers, 40 of children suffered primary generalized tonic-clonic fits. Behavior problems were measured by the mother's report on the child behavior rating checklist for the last 6 months prior to the first seizure. They reported that 22.8% of the epileptic children had suffered behavior problems possibly due to underlying neurologic dysfunctions. (21)

Neurodevelopmental and motor functions before initiation of AED's

In this study, non-significant increases of the scores of QNST were recorded in epileptic children suffering generalized tonic-clonic fits of primary (idiopathic) origin before initiation of AED therapy as compared to normal controls. This indicates no or minimal neurodevelopmental and motor derrangement in these epileptic children.

This is comparable to the results of Nasr et al (1993) who studied 35 Egyptian children suffering from idiopathic generalized tonic-clonic seizures and before the start of AED therapy. The Lauria-Nebraska scale utilized in testing these children includes several subtests comparable to those in our Quick Neuroloical Screening Test (QNST). They suggested that children with idiopathic generalized tonic clonic epilepsy did not differ from healthy children as regards performance of gross motor and tactile functions. However, they also reported poor performance in writing ability which measures fine motor accuracy. (15)

This reflects a selective nature of impairment of neurodevelopmental functions in children with grand mal epilepsy with evident derramgement as the complexity of the task increases. According to A.M. Kamel's model (1993, 1999)

epilepsy impair booting mechanism between coritical and subcortical brain centers, which is very important in cognitive and behavioural functions.

Neurodevelopmental & Motor functions After initiation of AED therapy

In the present work, further significant increases of the scores of QNST were detected in children treated with PHT&PB as compared to controls and to the other two groups treated with CBZ or VPA indicating more neurodevelopmental and motor derangement in the first two groups with significant correlation with serum levels.

Our results agree with those of May et al (1997) who studied children suffering tonic-clonic fits and reported bad effects of PHT treatment for 6 months on some psychomotor functions as demonstrated by tapping test and pursuit rotor with the dominant hand. Moreover, they ascertained statistical improvement of these function one year after its withdrawal.[16]

Vining et al (1997) compared the psychomotor effects of PB & VPA in children with idiopathic generalized tonic-clonic epilepsy using some neuromtor stigmata as Maze test which tests fine motor control, Ballistic Finger Tapping and Ambulation Backward which tests balance and coordination. They also used the Seashore rhythm tests which tests perception and accuracy in integration and reaction time. Comparing PB with VPA, they proved that PB treatment for 6 months had deleterious effects on these functions denoting derrangement of motor & neurodevelopmental functions in children with grand mal epilepsy receiving PB monotherapy but not in these receiving VPA montherapy.[8]

On the other hand, our results showed significant decrease of the score of QNST (i.e. improvement of neurobehavioral and developmental motor functions in children with idiopathic generalized tonic-clonic epilepsy who received CBZ & VPA monotherapy.

This accords with the results of O'Doughetry et al (1988)

who studied epileptic children with generalized idiopathic tonic-clonic type. They suggested a mild beneficial effect of CBZ therapy for 6 months on speeded hand – eye coordination and at low drug levels, more rapid processing items of memory occur.(7)

Also in agreement with our results are those of Aman et al (1990) who studied 25 children with idiopathic tonic-clonic epilepsy. All children were of normal I.Q's and attended normal classes. Procedures used test psychomotor performance were pursuit rotor task, seat movement. They found that CBZ treatment for 3 months caused an improvement in their motor steadiness and coordination (17)

In agreement also with our results are those of Sabers (1990) who studied the effect of VPA montherapy on 11 epileptic children with primary generalized tonic – clonic fits and found that children who started VPA monotherapy improved as regards motor speed and attentional psychomotor abilities.(18) Also, they found that patients suffered behavior problems possibly due to underlying neurologic dysfunctions. (21)

Using positron emission tomography (PET) & radioactive labeled oxygen, Trimble et al. (22) found that regional cerebral blood flow and (Basal metabolic oxygen. consumption (BMO_2) were lower in most regions especially in frontal and temporal cortices and basal ganglia specially in the left side in epileptic patients with behavioral disturbances.

The results (table 6) shows that carbamazepine and volproate helps in booting the functional intersection of ALP and PLP (kamal, A.M. 1993).

Rakhawy (1994) explained the behavioral disturbances associating epilepsy by his assumption that epilepsy and behavioral disturbances disorders are different clinical manifestations of the same brain cellular, chemical or physical pathology.(23)

Okasha (1995) suggested that the complexity and mis-interpretations arising at the post-ictal confusion state may prepare the ground for a later psychotic development. He also suggested that biologic antagonism in the form of an increase of

central monamine activity may raise the threshold to seizures while having a deleterious effect on behavior.[24]

Also, disturbed hippocampal, striatal and limbic system theta activity and limbic system kindling may be responsible for this deterioration as evidenced by Meador et al (1991) who found increased frequency, amplitude and rhythmicity of theta activity across the hippocampus, striation & limbic system[25].

Phenytoin (PHT) therapy

Results of the present study demonstrated a significant decline of behavioral functions in epileptic children receiving PHT monotherapy as manifested by the significant decrease of the Adjustment Seale for Children with direct association with serum levels of the drug.

This agrees with Pruitt et al (1985) who reported that PHT was associated with unsteadiness and involuntary movements in epileptic children[26].

Also, Herranz et al (1988) studied 78 children with primary generalized tonic-clonic epilepsy, aged <15 years of age for the behavioral side effects of PHT and other AED's every 3 months for 2 years. They found that generally side effects requiring to stop PHT or to change it were recorded in 20 of cases. Neurobehavioral side effects were recorded : in 6.3%, restless and short sleep in 6.3%, drowsiness in 1.6%, difficulty in getting asleep in 1.6%, nystagmus in 7.5% dizziness in 1.6% and headache in 1.6% They compared these side effects in patients receiving PB, CBZ & VPA and concluded that the worst tolerated was PHT and the best tolerated was CBZ[27].

Berlin et al (1995) studied 63 epileptic children, 40 of them suffered generalized tonic-clonic fits of idiopathic origin. They found that before initiation of therapy, behavioral disturbances were reported in 20-30% of them both before initiation of treatment and after its cessation. They added that PHT caused further behavioral disturbances as follows: emotional instability

in 16, irritability in 6, restlessness and short sleep in 6, hyperactivity in 3 and drowsiness in 2 cases (i.e. 33 cases totally)[28].

Sudha et al (1995) explained the PHT- induced impairment of behavioral functions by the decreased acetylcholine esterase enzyme activity in the hippocampus, cerebellum & cropus striatum[29].

Phenobarbital (PH)

In the present work, there was significant deterioration of behavioral tasks in all behavioral scales in epileptic children receiving PB as compared to controls and to the other two groups receiving CBZ & VPA (see. Tab. 5) Significant correlation between this deterioration and the drug serum level was found.

Pruitt et al (1985) reported that the incidence of behavioral disturbances in children who were taking PB has ranged from 9% to 75%. Hyperactivity was the most commonly recognized disturbance in addition to fussiness, lethargy, disturbed sleep (walking in the middle of the night) irritability, disobedience and depressive symptoms.

Vining et al (1997) studied 9 children with idiopathic generalized tonic-clonic epilepsy (5 if them receiving PB & 4 receiving VPA). Their behavioral patterns were assessed by the Burk's Behavior Rating Scale. Abbott's Parent's Questionnaire and Abbott's Teachers Questionnaire. They found that epileptic children on PB regimen were significantly more hyperactive than VPA treated patients with more complaints of aches. Children with PB-regimen suffered from significant problems of behavior as disobedience, problems of sleep, problems with friends and were basically unhappy[8].

Brent et al (1987) studied a sample of 9 children who suffered primary generalized tonic-clonic fits. 5 were treated with PB and 4 with CBZ. They ascertained the prevalence and severity of depressive disorders and anxiety in epileptic children treated with PB in comparison with CBZ which showed its good antidepressant properties in children treated with it or shifted to it from other montherapy or polytherapy.

Herranz et al (1988) studied 49 children with generalized

tonic-clonic epilepsy of primary origin and receiving PB montherapy for behavioral effects using clinical assessment data and parental questionnaire. Two years follow up with 3 months interval reassessment. They reported a very high incidence of behavioral disturbances in patients receiving PB 60.6% behavioral disturbances in general 24.2% irritability 24.2% restlessness and short sleep. 22.2% hyperactivity, 11.1% difficulty in getting asleep, 7.1% drowsiness 2% aggressiveness presented in patients receiving PB were minimal as 3% ataxia, 1% tremors & 1% dizziness. So, they concluded that the most deleterious effects of PB are behavioral ones[27].

The bad effects of PB could be explained by decreasing neurotransmitters release and post-synaptic excitation by blocking Ca^{+2} entry into neurones by its greatest maximal enhancement of GABA responses[31].

In this work, the effects of CBZ & VPA on behavior were favorable and psychological testing showed significant improvement in most tasks examining behavior as behavioral part of H.N scale and Adjustment scale. Improvement in behavioral functions was positively correlated with the therapeutic serum drug level.

Rett (1994) examined 20 children with generalized tonic-clonic epilepsy of primary origin, subdivided into two equal subgroups:

The first was 10 children receiving varying anti-convulsants and shifted to CBZ monotherapy either due to poor seizure control or due to bad side effects.

The second group was 10 children who had never been treated before and started CBZ monotherapy. Rett used Rorsasach's test which measures affectivity, activity and psychic manifestations. I.Q's of these children using WISC-R, were within normal range with improvement after CBZ therapy. Rett proved trend towards significant improvement in both subgroups with complete seizure control[32].

Berlin et al (1995) ascertained a significant beneficial

effect on mood and behavior of CBZ in epileptic children. After 12 months of therapy, complete seizure control and antidepressant properties of CBZ were documented in these children.

Herranz et al found better and longer sleep in 5.4% of cases, with minimal behavioral side effects in 15% of cases in the form of drowsiness, irritability, restlessness, hyperactivity, aggressiveness and feeling tired. They concluded that that 57% of children had no side effects, while 8% required to stop the drug because of some digestive side effects[27].

Stores et al (1992) compared the behavioral effects of VPA & CBZ monotherapy in 20 children with primary generalized tonic-clonic epilepsy, with 47 nonepileptic, children receiving the drug as psychotropic agent. Eight epileptic children started CBZ while 12 started VPA. Children were examined by behavioral tests as Conner's Parents Questionnair (CPQ) and Conner's Teachers Questionnaire (CTQ). They followed epileptic children for 12 months. They found that both drugs were effective in most cases as regards seizure control without causing psychological effects. Improved behavioral functions was the same in children with epilepsy receiving both drugs and non epileptic controls[33].

Mohmoud et al (1995) explained the beneficial effects of VPA & CBZ on behavioral functions by:

1- GABA – ergic effects:
   (i) Increasing GABA – ergic neuro-transmission.
   (ii) Regulation of GABA-b receptors which modulate noradrenergic activity which plays an important role in bipolar affective disorders.
2- Reduction of glutamted decarboxy activity in frontal cortex.
3- Reduction of GABA in ecrbro-spinal fluids.
4- Anti-kindling properties[34].

Cognitive functions before Initiation of AED therapy

In the present work, epileptic children before initiation of AED therapy, performed poorly on many scales and showed

significant impairment of cognitive functions as manifested by lower score performance (Table. No. 3) on WISC-R, lower scores of performance of H.N. scale (table No. 2), when compared to healthy controls. This deterioration and poor performance were directly proportionate to the duration of illness and the frequency of seizures.

This agrees with the results of Mitchell et al (1992) who studied reaction times, attention and impulsivity in untreated children with idiopathic generalized tonic-clonic fits. They found that untreated epileptic children were significantly slower, more variable and made more omission errors than control children even when analysis was limited to epileptic children with I.Q's greater than 90. they found that these children did not make more commission errors (ie. impulsive errors)[35].

Our results are also in agreement with those of Nasr et al (1993) who studied a group of Egyptian children suffering primary generalized tonic-clonic epilepsy before initiation of AED therapy. Tools used in their study covered nearly all cognitive functions and learning abilities. They reported that those children had poorer performance than controls on the visual scale and in all scales that assess linguistic abilities. They also found that these children had significantly poorer performance on all scales that assess academic functions as the arithmetic, writing and reading scales. Concerning memory function, they found that grand mal epileptic children showed significant poorer performances on short and long-term memory scales as compared to normal controls[15].

Camfield et al (1993) reported that in children with recent onset generalized tonic-clonic epilepsy, at the time of diagnosis and before initiation of therapy, learning disorders and cognitive disturbances were present as determined by the attending neurologist and psychiatrist who used the clinical data available including school reports, and psychometric testing [36].

In a study of Mandelbaum and Burack (1997) they investigated the cognitive and behavioral profiles of 43 children

aged from 4 to 16 year, with recent onset idiopathic seizures. The children were of average intelligence. They found that children with generalized tonic-clonic convulsions perform poorer than children with partial seizures but better than those with absence seizures before initiation of therapy and as compared to normal controls[37].

This deterioration of cognitive and intellectual functions in freshly diagnosed cases of primary generalized tonic – clonic fits could be explained by the transient and prolonged cognitive impairing effects of sub-clinical EEG epileptiform discharges which precede and associated the emergence of clinical seizure (Aldencamp et al, 1996 and Casaro & Collino, 1997).[38,39]

Cognitive functions after Phenytion (PHT) therapy

In this work, PHT was found to be associated with impairment of performance across several measures of cognitive abilities related to memory, mental and motor speed & I,Q's as evidenced in HN scale: (performance part), reaction times, achievement scores (in Arabic language, arithmetics and total achievement score) and WICS-R. Significant negative correlation was found between serum level of the drug and the degree of deterioration of test performance on several measures.

This aggress with the conclusions of Pruitt et al (1985) who mentioned that PHT therapy caused deficits in neuro-psychological tests as impaired attention, problem-solving & visuomotor tasks[26].

Also, Trimble (1991) stated that PHT therapy for 2 years significantly impaired performance in a variety of tasks and in several subjects, a significant relationship between impairment and serum levels was recorded[40].

Our results are also in agreement with those of Nasr et al (1993) who studied a group of children suffering primary generalized tonic-clonic epilepsy and receiving PHT monotherapy for 6 months using Lauria-Nebraska scale. They proved disturbed general intellectual level, reasoning ability, attention, linguistic abilities, academic skills & memory[15].

Cognitive functions after Phenobarbital (PB) monotherapy

In this study, PB caused impaired performance on various measures of cognitive functions as performance part of HN Scale reaction times, achievement scores and WISC-R with direct association with serum levels.

This agrees with the results of Vining et al (1987) who studied 7 children with generalized tonic-clonic epilepsy of primary origin and receiving PB for, 6 months. They used WISC-R and other tests for learning & cognition. They found deterioration of all cognitive, intellectual and learning parameters in PB-treated group as compared to VPA treated group.

Comparable results were obtained by Calendre et al (1990) who applied Wechsler intelligence scale for Children – Revised (WISC-R) in 64 epileptic children and 60 healthy children as controls, they concluded that long-term PB treatment for 9-12 months induces a significant impairment in learning ability whereas long term valproate therapy does not exert a noticeable noxious effect in this respect[41].

Also in agreement with our results are those obtained by Nasr et al (1993) who found deterioration of performance on most tasks of Lauria- Nebraska scale testing intellectual and learning abilities in children receiving PB as long – term anti-epileptic[15].

These bad effects of PB on cognitive abilities could be explained by its reducing effect on local cerebral blood glucose metabolism. Increased regional cerebral blood glucose (rCBGL) metabolism is an important indicator of neuronal activity.

Leiderman (1991) reported a statistically significant relationship between the local blood glucose metabolism and the reduced scores on the intelligence scale in epileptic patients receiving AED's. PB reduced cerebral glucose metabolism by 37%, PHT reduced it by 13% while VPA caused only 1.2% reduction[42].

Cognitive functions following Carbamazepine (CBZ) and Valproate (VPA) monotherapy

In this study, the effects of CBZ VPA on cognitive functions and intellectual abilities were favorable and the various tests showed apparent significant improvement in all tasks in children receiving CBZ as monotherapy for primary generalized tonic-clonic epilepsy. The improvement in all tasks in children receiving CBZ as monotherapy for primary generalized tonic-clonic epilepsy. The improvement in cognitive functions was positively correlated with serum CBZ levels.

Our results agree with the review by Trimble (1990) who stated that many studies documented improvement in cognitive functions when children were given CBZ in addition to their existing drug regimen or when they were switched from barbiturates or polytherapy to CBZ monotherapy[40].

Sabers (1990) found that significantly improved verbal learning and retention and attention /psychomotor speed 4 months following CBZ monotherapy[18].

Also, in agreement with our results are those obtained by Aman et al (1990) who studied the effects of CBZ on the cognitive functions in 25 children with idiopathic generalized tonic-clonic epilepsy and 50 voulunteer non-epileptic children. CBZ treated epileptic children showed no deterioration of cognitive functions when compared to normal controls. Moreover they showed significant improvement of these functions when CBZ reached its trough concentration[17].

Also, in agreement with our results are those of Nasr et al (1993) previously discussed who concluded that CBZ had a beneficial effect on intellectual and cognitive performance in children with primary generalized tonic- clonic epilepsy and receiving CBZ as an AED monotherapy[15].Also, Mitchell et al (1993) studied 35 children receiving CBZ and concluded that CBZ had a dose – dependent improving effect on cognitive performance specially reaction time, attention and impulsivity when used as monotherapy at therapeutic levels.

Mahmoud et al (1995) explained the beneficial effect of CBZ on cognitive functions by:

1- Inhibition of glutamate release via blockade of Na^+ channels.
2- Structural resemblance to tricyclic anti-depressants.
3- Reduction of GABA turn-over.
4- Antikindling properties[34].

Stores et al (1992) studied 20 school children with newly diagnosed primary generalized tonic – clonic epilepsy before and after CBZ treatment (n=12).

They assessed the general intellectual functions and specific abilities by a selected battery of tests. They found that after 12 months of treatment with either CBZ or VPA, no significant differences were seen in any comparison between any treatment group and the normal controls for any of the general measures of intelligence and attainment[33].

Recommendations

1- Epileptic children should be studied by multi-disciplinary approach to define their psychological and cognitive profiles.
2- Social and cognitive outcome of epilepsy could be improved by changing the family, teacher's and social attitudes towards epilepsy and by early diagnosis and treatment by the appropriate AED.
3- PHT & PB had deleterious effects on cognition and behavior and their prescription should be restricted to cases resistant to other medications.
4- CBZ & VPA had beneficial effects on cognition and behavior and so are preferable over PHT & PB.
5- AED's seum level monitoring is a must to reach the optimal therapeutic level without causing serious side effects especially on cognition & behavior.
6- Epilepsy clinics should be supplied by the suitable batteries and scales to study the target cognitive and behavioral functions by the qualified psychiatrist.
7- Genetic counseling, early diagnosis and treatment with

"good" AED and psychosocial support could reduce the untoward associates in children with epilepsy.

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