# *Psychiatric Co-morbidity with Epilepsy in Children and Adolescents*

***Thesis***

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# ***Introduction***

Epilepsy is the name of a brain disorder characterized predominately by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures. Epilepsy is not a singular disease entity but a variety of disorders reflecting underlying brain dysfunction that may result from many different causes ***(Fisher et al., 2005).*** Epilepsy is a heterogeneous disorder that consists of clinical syndromes, characterized by different types of seizures, underlying etiologies, diagnostic criteria, treatment strategies, and longitudinal outcomes ***(Shinnar & Pellock, 2002).***

Little common agreement exists on the definition of the terms seizure and epilepsy. The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) present practical and operational definitions applicable both in medical and non-medical settings (Table 1) ***(Fisher et al., 2005).***

**Table (1): Definitions**

| |
|---|
| ***Epileptic seizure:*** is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. |
| ***Epilepsy:*** is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. |

The International League Against Epilepsy and the International Bureau for Epilepsy described seizure as a transient event of signs and symptoms due to abnormal neuronal activity in the brain. An epileptic seizure is transient, demarcated in time, with a clear start and finish. Termination of an epileptic seizure often is less evident than is the onset, because symptoms of the postictal state can blur the end of the seizure ***(Fisher et al., 2005).***

Seizures are classified into generalized (bilateral) and focal (partial). Generalized seizures involve both hemispheres of the brain and can be tonic, clonic, tonic-clonic, and myoclonic. Generalized non-convulsive seizures are absence seizures. Focal seizures originate from a focal area in one cerebral hemisphere and may or may not have secondary generalization later ***(Blume et al., 2001).*** The multiple seizure types characterize childhood-onset epilepsy and they may evolve from one type to another during the course of illness (Table 2) ***(Cowan, 2002).***

**Table (2): Epileptic seizure types & precipitating stimuli for reflex seizures *(Engel, 2001)***

| **Self-limited seizure types** |
|---|
| • *Generalized seizures*<br>o Tonic-Clonic seizures (includes variations beginning with a clonic or myoclonic phase)<br>o Clonic seizures (with or without tonic features)<br>o Typical absence seizures<br>o Atypical absence seizures<br>o Myoclonic absence seizures<br>o Tonic seizures |

- Spasms
- Myoclonic seizures
- Eyelid myoclonia (with or without absences)
- Myoclonic atonic seizures
- Negative myoclonus
- Atonic seizures
- Reflex seizures in generalized epilepsy syndromes

- *Focal seizures*
  - Focal sensory seizures
    - With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)
    - With experiential sensory symptoms (e.g., temporo-parietalo-occipital junction seizures)
  - Focal motor seizures
    - With elementary clonic motor signs
    - With asymmetric tonic motor seizures (e.g., supplementary motor seizures)
    - With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)
    - With hyperkinetic automatisms
    - With focal negative myoclonus
    - With inhibitory motor seizures
  - Gelastic seizures
  - Hemiclonic seizures
  - Secondarily generalized seizures
  - Reflex seizures in focal epilepsy syndromes

**Continous seizure types**

- *Generalized status epilepticus*
  - Generalized tonic-clonic status epilepticus
  - Clonic status epilepticus
  - Absence status epilepticus
  - Tonic status epilepticus
  - Myoclonic status epilepticus

- *Focal status epilepticus*
  - Epilepsia partialis continua
  - Aura continua
  - Limbic status epilepticus (psychomotor status)
  - Hemiconvulsive status with hemiparesis

**Precipitating stimuli for reflex seizures:**

- Visual stimuli
  - Flickering light
  - Patterns
  - Other visual stimuli
- Thinking
- Music
- Eating
- Praxis
- Somatosensory
- Proprioceptive
- Reading
- Hot water
- Startle

An epileptic seizure is a clinical event. Detailed specification of subjective and objective clinical phenomena during an epileptic seizure is difficult, because of the wide range of possible manifestations. Seizure presentation depends on location of onset in the brain, patterns of propagation, maturity of the brain, confounding disease processes, sleep-wake cycle, medications, and a variety of other factors. Seizure can affect sensory, motor, and autonomic function; consciousness; emotional state; memory; cognition; or behavior ***(Fisher et al., 2005).***

Not all seizures affect all of the previous factors, but all influence at least one. In this context, sensory manifestations are taken to include somato-sensory, auditory, visual, olfactory, gustatory, and vestibular senses, and also more complex internal sensations consisting of complex perceptual distortions. In previous definitions, these complex internal sensations were referred to as psychic manifestations of seizures. Some seizures manifest as fear, elation, satisfaction, anxiety, or other subjective sensation ***(Fisher et al., 2005).***

***Autonomic symptoms in childhood epilepsy:***

Autonomic symptoms (ASs) described in adults: respiratory (hyperventilation, apnea, bradypnea, dyspnea, cyanosis, postictal coughing); gastrointestinal (epigastric aura, nausea, vomiting, spitting, hypersalivation, belch, and hiccup); cutaneous (flushing, pallor, piloerection); pupillary (mydriasis, miosis); and urinary (ictal urinary urge) manifestations ***(Baumgartner et al., 2001).***

Among the ASs described in adults, cyanosis, pallor, pilomotor seizure, mydriasis, and urinary urge were not observed in children. Fogarasi et al. study shows that ASs are common in childhood focal epilepsies appearing already in infants and young children (***Fogarasi et al., 2006).***

**Respiratory manifestations:** Hyperventilation is a frequently reported symptom of partial seizures. It can be found in both frontal and temporal lobe epilepsies, occurring

more frequently in mesial compared with neocortical temporal lobe seizures. Increased upper-airway secretion during seizures might result in early postictal reactive coughing. Study results showed temporal dominance in postictal coughing. Its high frequency and age-independent appearance make this easily observable phenomenon a clinically important AS of childhood partial seizures ***(Fogarasi et al., 2006).***

**Gastrointestinal manifestations:** Epigastric auras are most frequently encountered in TLE. Electrical-stimulation studies showed that a sensation similar to epigastric aura can be elicited from the hippocampus, amygdala, and insula, as well as the basal ganglia and thalamus. Epigastric auras were reported with both left- and right-sided epilepsies. Ictal vomiting was associated with medial and lateral temporal lobe seizures and with spread to the superior lateral temporal region. Epigastric aura and ictal vomiting are usually medial TLE symptoms rather temporal lateral sign ***(Fogarasi et al., 2006).***

Peri-ictal ASs showed a strong relation to the temporal lobe and its functional networks. Although the human autonomic network includes several parts of the brain (hypothalamus, insula, medial prefrontal cortex, amygdala, periaqueductal gray matter, parabrachial complex, nucleus tractus solitarius, and the ventrolateral medulla), the mechanism by which partial seizures cause ASs is thought to be spread by an ictal discharge from cortex to the richly

connected hypothalamus. Thus the richness of limbic–hypothalamic connections also might account for the prominence of ASs of temporal lobe seizures in children ***(Fogarasi et al., 2006).***

***Ictal emotional expressions in childhood epilepsy:***

Emotional expression (EEs) described in adults: smile, laughing, happiness, surprise, fear, pain, crying, anger, disgust, and sadness. Emotional elements included both objective signs (e.g., reporting of a happy emotion by the patients) and subjective symptoms (e.g., fearful face expression). Among the other EEs described in adults, surprise, anger, disgust, and sadness were not observed during childhood seizures. No child showed both positive and negative ictal emotions ***(Fogarasi et al., 2007).***

Fogarasi et al. showed that ictal EEs are relatively frequent and easy to recognize in childhood ***(Fogarasi et al., 2007).*** The most frequently assessed EEs of adult partial seizures were negative emotions including psychic aura and ictal fear. Clinical studies found that seizure associated fear is most frequently originated from the temporal lobe or temporal lobe association cortex ***(Cendes et al., 2005).*** it was also noted that behavioral modifications suggestive of intense fear or aggression were related to the frontal lobe ***(Bartolomei et al., 2005)***, or at least to the involvement of fronto-temporal neural networks ***(Tassinari et al., 2005).***

In contrast, EEs appeared more frequently during extratemporal than temporal lobe seizures in our children. Assessing subgroups, positive EEs were more likely extratemporal while negative emotions did not localize the seizure onset zone. This age-dependent difference supports the hypothesis that, although the limbic system is one of the earliest cortical regions to fully mature the development of its neural connectivity is incomplete before adolescence ***(Fogarasi et al., 2002).***

Assessing the lateralizing value of childhood ictal EEs, we found that positive emotions appeared more frequently during right-sided seizures while negative emotions did not lateralize the seizure onset zone ***(Stefan et al., 2004).*** According to an infantile clinical study, however, positive emotional expression (smile) in 5–12-month-old babies was controlled by the right hemisphere ***(Holowka & Petitto, 2002).***

Results of different studies suggest that hemispheric lateralization of emotions is different between children and adults. Emotion is a multi-componential set of phenomena which can be unraveled only by careful examination of relations between neuro-physiological changes and specific emotion subcomponents ***(Fogarasi et al., 2007).***

Patients with recurrent seizures may have a normal scalp EEG between seizures and even during seizures. However, EEG discharges during epileptic seizures are

orderly and relatively stereotyped. Firing of neurons may involve inhibition as well as excitation, so it is not always the case that an epileptic seizure involves an excess of excitation over inhibition. A feature more common to epileptic seizures is abnormal enhanced synchrony of neurons ***(Fisher et al., 2005).***

Cerebral cortex is the primary element in the generation of epileptic seizures, but it is not the only one. In some circumstances, epileptic seizures can originate in thalamocortical interactive systems or in the brainstem ***(Fisher et al., 2005).***

At least one seizure is required to establish the presence of epilepsy; a predisposition, as determined, for example, by a family history, or by the presence of epileptiform EEG changes, is not sufficient to determine epilepsy ***(Fisher et al., 2005).***

People with epilepsy, behavioral disturbance, such as interictal and postictal cognitive problems, can be part of the epileptic condition. Patients with epilepsy may suffer from stigma, exclusion, restrictions, overprotection, and isolation, which also become part of the epileptic condition. Seizures and the potential for recurrence of seizures also often have psychological consequences for the patient and for the family ***(Fisher et al., 2005).***

Epilepsy is the most common pediatric neurological disorder. Of note, febrile seizures, the most common type of seizures in children, are not considered epilepsy. The prevalence of epilepsy is about 0.5% to 1% of all children from birth to 16 years of age. Children are at highest risk for developing seizures in their first year of life, and the median age of seizure onset is between 5 and 6 years. In neurologically normal children focal seizures occur in about 59% of cases, generalized seizures in 29%, and about 12% have an undetermined type ***(Shinnar & Pellock, 2002).***

There are multiple factors that bear on development of children with epilepsy that depend on the time of seizure diagnosis, the presence of other existing medical conditions and social circumstances within families. Epilepsy is not a singular condition and can occur from birth or have its onset anytime during development, and can result from associated medical conditions that include metabolic disorders, brain malformations from migrational or anomalous vascular defects or late consequences of infections or trauma ***(Leonard & George, 1999).***

Epilepsy is a disorder that involves a constellation of symptoms that vary in frequency and intensity from child to child. Of those children with epilepsy, approximately 25% continue to experience poor seizure control even with anti-epileptic drug therapy. In addition, it is well documented that epilepsy in children is associated with problems in multiple areas, including academic achievement, behavioral

and emotional adjustment, and social competence. Even when seizures are well controlled with antiepileptic medications, these problems may persist because of abnormal brain formation or function, continuing epileptic activity in the brain (without symptoms), or side-effects from antiepileptic medications ***(Elliot et al., 2004).***

The timing of seizure onset is important in evaluating cognitive and psychosocial factors that influence developmental outcome. Febrile seizures during early childhood may be associated with later occurring complex partial seizures and mesial temporal sclerosis. These factors, thus, predispose children to seizure onset at varying development stages, where impact is appreciated as a consequence of developmental aberration during periods of active brain maturation and exert differential effects on development depending on the age of onset ***(Leonard & George, 1999).***

Beckung and Uvebranttitled titled their 1997 paper on epilepsy "Hidden dysfunction in childhood epilepsy". "Hidden" and "under the surface" may be, but from whom? Young people with epilepsy and their parents have been well aware for many years of some of these associated problems. But health professionals presented with children with epilepsy have concentrated too much on the convulsive episode itself and ignored the broader spectrum. About third of children with epilepsy have another easily recognizable pathology, such as severe learning disabilities, yet number of

children who have specific learning disabilities (e.g. dyslexia) and behavioral problems is less clear ***(Bax, 1999).***

It is not known when behavior problems begin in children with epilepsy, though it has usually been assumed that they begin after the diagnosis of epilepsy. Factors accounting for these behavior problems also have not been well delineated. Presumed causes include effects of seizures, effects of antiepilepsy medication, poor child and family adaptation to seizures, and neurologic dysfunction that brings about both seizures and behavior problems ***(Austin et al., 2001).***

The sequential relationship between the onset of seizures and the development of psychiatric problems is unknown. It was reported that up to 45% of children have emotional and behavioral problems before the onset of epileptic seizures. The identified pre-existing psycho-pathology may be an early representation of an epilepsy syndrome characterized by seizures and psychopathology. On the other hand, pre-existing emotional problems may be unrelated to epilepsy and may represent an independent co-morbid condition ***(Plioplys, 2003a).***

## *The role of electroencephalography (EEG) and neuroimaging in dealing with epileptic patients:*

### Electroencephalography:

EEG is an essential clinical diagnostic tool, but it is very important not to over or under estimate the information given by EEG. Thus knowing the value of EEG and its limitation is very important ***(Chokroverty, 1995; Gaber et al., 2000).***

### Value of EEG:

**a) A diagnostic tool:**

The most important value of EEG is providing signs of epilepsy. Epileptiform abnormalities are certain wave forms considered of potentially epileptogenic significance. These are spikes, sharp waves, spike and waves and sharp and slow waves complexes. EEG is also essential in diagnosing the type of epilepsy and classifying it according to the International League Against Epilepsy e.g. childhood absence and juvenile myoclonic epilepsy ***(Chokroverty, 1995; Gaber et al., 2000).***

**b) A prognostic tool:**

EEG can provide idea about the prognosis of epilepsy. It can help in evaluating the reasons for patient's behavioral disturbances. Focal or diffuse slow waves in the EEG accompanied by spikes or sharp waves may be secondary to repeated seizures. Excessive slow waves in the EEG may

indicate overmedication. The value of EEG monitoring in predicting the chances of recurrence of seizures after AED withdrawal in patients who remain seizure free 2-4 years remains controversial ***(Chokroverty, 1995; Gaber et al., 2000).***

**c) Management decision:**

EEG plays an important role in management decisions in the following situations ***(Chokroverty, 1995; Gaber et al., 2000)***:

1. In determining the type of pharmacotherapy in epilepsy, which depends on type of epilepsy and epileptic syndrome.
2. In assessing the effects of AEDs on the clinical outcome.
3. In documenting the undesirable side effects of AEDs on the EEG recording.
4. In assessing the possibility of recurrence after withdrawal of AEDs.

**<u>Limitations of EEG:</u>**

**a) A diagnostic tool:**

Normal EEG findings do not exclude a diagnosis of epilepsy. This is because epilepsy is a paroxysmal disorder, therefore, during the short recording (20-30 min) paroxysmal epileptiform discharges are not necessarily seen. Hence, on repeating the EEG, there is better chance for getting positive interictal findings. The initial EEG may show normal results in 50% of true epileptics. Even after 3-4 EEG recordings 8-10% remain normal ***(Chokroverty, 1995; Gaber et al., 2000).***

The second reason for obtaining normal EEG results in a patient with true epilepsy is that the discharging focus is in a deep location or buried in a sulcus and therefore inaccessible to surface EEG recording ***(Chokroverty, 1995; Gaber et al., 2000).***

Rarely, ictal EEG may not be diagnostic. This is true in patients with simple partial seizures with motor manifestations some patients with partial complex seizures with only psychic manifestations does not have ictal scalp findings ***(Chokroverty, 1995; Gaber et al., 2000).***

Other errors may arise as well. Extracranial EEG recordings in some cases of complex partial seizures may falsely localize or lateralize the epileptic foci as documented by depth recording ***(Chokroverty, 1995; Gaber et al., 2000).***

**b) A prognostic tool:**

There is no clear relationship between EEG epileptiform discharges and the clinical improvement in the epileptic attacks as well as the serum levels of antiepileptic drugs (AEDs) except in absence spells. With some AEDs as carbamazepine, the EEG epileptiform abnormalities may increase and the background activities may show slowing in the presence of clear improvement of clinical spells ***(Chokroverty, 1995; Gaber et al., 2000).***

**Neuroimaging:**

**a) Computed Tomography Scan (C.T):**

Computed tomography has made it possible to detect morphological information of gross brain changes, but to a lesser extent minimal brain changes such as mesial temporal sclerosis. For such a reason it was concluded that C.T scan is of little or no use in the diagnosis of complex partial seizures as it showed pathological findings only in 58.4% of patients with complex partial seizures. C.T scan was found to be unreliable in detecting microscopic changes in temporal lobe ***(Haan and Deppe, 1984; Gaber et al., 2000).***

However, there are few advantages of C.T scan such as shorter acquisition time which is significant in examining restless patients, demonstration of details in cortical bones and calcified lesions ***(Mosley and Sutton, 1992; Gaber et al., 2000).***

**b) Magnetic Resonance Imaging (MRI):**

The rapid progress and evolution of MRI has recently obligated most authors dealing with epilepsy studies to diminish or ignore the use of C.T scanning, particularly in complex partial seizures. MRI could detect the following in patients with temporal lobe epilepsy: small temporal lobe, small mesial temporal structures, small hemisphere and focal mesial temporal hyper-intense signals ***(Mclachlan et al., 1985; Adam et al., 1992; Gaber et al., 2000).***

MRI can show temporal lobe abnormalities not detected by C.T and corresponding to the site of epileptogenic focus. This is because lesions in the inferior temporal lobe may not apparent on C.T because of bone hardening artifacts ***(Gaber et al., 2000).***

Minimum requirements of MRI ***(ILAE Neuroimaging Commission, 1997)***:
In countries where MRI is not readily available minimum requirements of MRI are:

- Patients with partial or secondary generalized seizures and apparently generalized seizures that do not remit with AED treatment.
- Patients who develop progressive neurological deficits.

## ***Aim of the work:***

The study is designed to :

1. Detect the difference between co-morbid psychiatric disorder in epileptic children and adolescents and healthy children; and whether is it related to different seizure variables or not.
2. Examine the relationship between self-reported anxiety and depression symptoms with demographic and seizure-related factors.
3. Differentiate between various types of disruptive behavior in epileptic children and adolescents.

# ***Pathophysiology of seizures and neuronal damage in epilepsy***

Brain maturation is an extremely well-orchestrated process consisting of multiple steps to ensure that targeted cells are generated with specific phenotypic properties in an orderly fashion ***(Marin & Rubenstein, 2001).*** The development of cortical circuitry is a dynamic and complex process whereby newborn neurons must generate precise connections with surrounding neurons to maintain the balance between excitation and inhibition. Of particular interest is the role of neurotransmitters in the regulation of activity-dependent mechanisms of synaptogenesis ***(Heck et al., 2007).***

The immature brain is highly excitable in order to support synaptogenesis and increased neuronal plasticity. Such increase of excitability is crucial for normal development but it can also participate in easy generation of seizures in the immature brain ***(Mareš & Kubová, 2008).*** The brain is most vulnerable to disruption during the prenatal and early postnatal periods when there is rapid growth and differentiation of neuronal populations. It is during this time that cells are born, migrate to their distant destinations, and integrate into the local circuitry of specific lamina of the neocortex ***(Marin et al., 2003).***

**The role of GABA and glutamate in brain development:**

During neural circuit development, simple, undifferentiated and unconnected cells grow into neurons, whose complex, three dimensional morphologies provide the structural basis for the precise synaptic connections that characterize the adult brain. A wealth of experimental data supports the view that this process is regulated by neuronal activity and neurotransmission. Pharmacological, genetic and molecular manipulations indicate that GABAergic neurons and GABAergic signaling are particularly important for brain development ***(Hensch & Stryker, 2004).***

During corticogenesis, the principal adult inhibitory neurotransmitter GABA influences the processes of cell proliferation, migration, and differentiation ***(Heck et al., 2007).*** GABAergic signaling has the unique property of 'ionic plasticity', which is based on short-term and long-term changes in the $Cl^-$ and $HCO_3^-$ ion concentrations in the postsynaptic neurons ***(Rivera et al., 2005).***

The role of GABA in early network activity of mammalian cortical structures during the developmental change is in the action of GABA from a depolarizing (and often excitatory) transmitter in immature neurons to a hyperpolarizing and typically inhibitory one. The key mechanism in such a change in transmitter function must be postsynaptic. In the case of GABA and its sister transmitter glycine, these mechanisms are based on the maturation of

neuronal $Cl^-$ homeostasis, which produces a negative shift in the equilibrium potential of $Cl^-$ during neuronal development and differentiation ***(Rivera et al., 2005).***

Since the discovery that GABA can depolarize the membrane potential of immature neurons, it has become clear that specialized features of GABAergic transmission enable it to serve multiple roles during development. Indeed, it appears that over the course of neural circuit formation, the maturational changes in GABAergic signaling parallel the changing requirements faced by developing neurons: first, they must take up the correct position in the tissue and begin to differentiate; second, they must establish their mature morphology and form synaptic contacts with other cells; and third, they must refine their connections to become part of a precise network. This is all achieved while balancing excitation and inhibition in such a way as to facilitate activity-dependent mechanisms, but not threaten the viability of the cell, for instance by excitotoxicity ***(Akerman & Cline, 2007).***

GABAergic transmission is characterized by several features that make it an ideal regulator of activity-dependent neuronal differentiation and circuit formation. First, GABAA receptors are not permeable to potentially dangerous ions such as calcium (Ca2+). Rather, GABAA receptors are primarily permeable to chloride ($Cl^-$), a relatively inert ion, which is not believed to have a role in intracellular signaling

events. Second, the resting intracellular $Cl^-$ concentration is controlled by developmental expression and activity-dependent regulation of $Cl^-$ transporter proteins ***(Fiumelli & Woodin, 2007).*** This can have dramatic effects on the ionic driving force and, therefore, the reversal potential of the GABAA receptor-mediated responses. This flexibility in how a neuron is affected by GABAergic inputs is not available to most other neurotransmitter systems. Third, neural circuits, such as feedforward and feedback GABAergic circuits, impose specific temporal rules on the timing of glutamatergic and GABAergic inputs and, therefore, on patterns of activity within and between brain circuits ***(Akerman & Cline, 2007).***

***GABA-ergic signaling during the establishment of neural circuits:***

In mature neurons, $GABA_A$ receptor activation increases membrane permeability to $Cl^-$ ions, which typically leads to a net inward flow of $Cl^-$ and hyperpolarization of the membrane potential. At early stages of development GABAA receptor activation depolarizes the cell membrane as a result of the immature expression pattern of the $Cl^-$ transporters NKCC1 and KCC2, which generates a positive $Cl^-$ reversal potential relative to the resting membrane potential ***(Ben-Ari, 2002).***

NKCC1, a sodium–potassium–chloride co-transporter, imports $Cl^-$ and is expressed from the embryonic stage until the first postnatal week. KCC2 is a potassium–chloride

cotransporter, exports $Cl^-$ and is weakly expressed at birth and upregulated as the brain matures ***(Wang & Kriegstein, 2008).*** Its expression is sufficient to generate hyperpolarizing responses to GABA, even in young neurons ***(Akerman & Cline, 2006)*** *(Figure 1)*. Although often referred to as a 'switch', the normal shift in GABAA receptor reversal potential takes several weeks to reach mature hyperpolarizing levels. Because GABA depolarizes immature neurons throughout the period of their morphological development and synaptogenesis, membrane depolarization in response to GABA probably represents a fundamental signaling mechanism regulating neuronal development and circuit assembly ***(Akerman & Cline, 2007).***

GABAergic signaling precedes glutamatergic signaling in the developing neocortex because newborn neurons express GABA-A receptors (GABAARs) and receive GABAergic inputs from striatally derived interneurons before forming glutamatergic synapses with each other ***(Wang and Kriegstein, 2008).***

In many brain regions, the first synaptic inputs of a neuron are GABAergic and early glutamatergic circuits can be relatively weak ***(Akerman and Cline, 2007).*** Depolarizing GABAergic inputs cooperate with NMDA receptor-dependent signaling during neuronal development ***(Ben-Ari, 2002).***

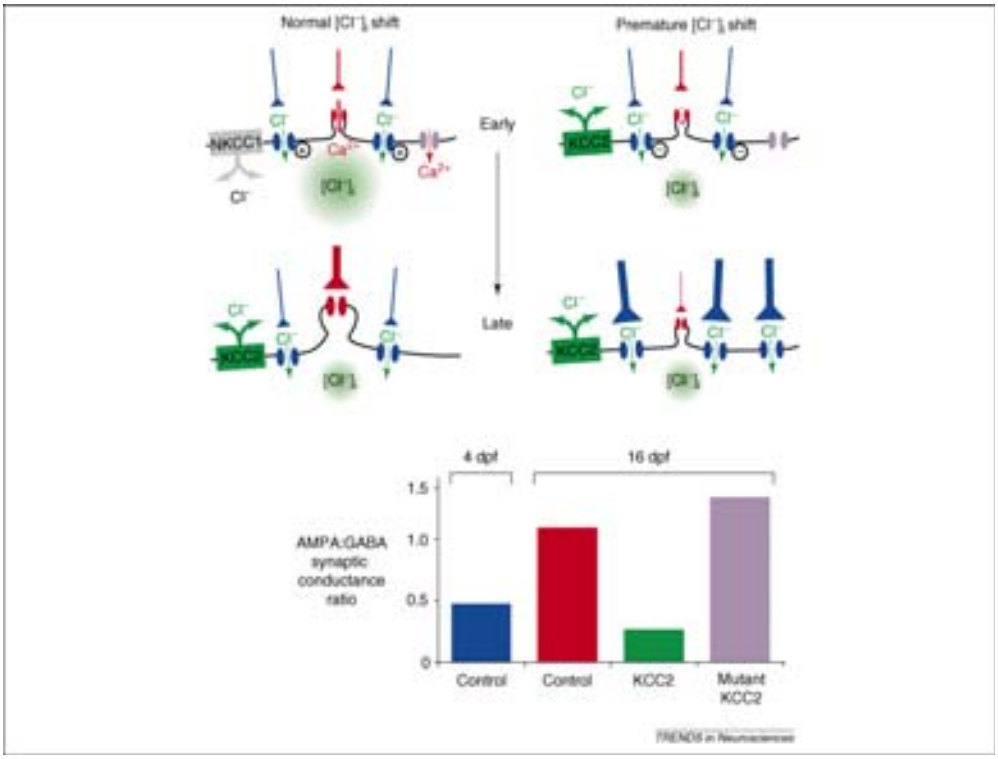



***Figure (1)*: Early depolarizing responses to GABA are required for the development of the normal ratio of excitatory to inhibitory synaptic input. At early stages of development, neurons receive relatively weak excitatory glutamatergic input (red) which increases with normal development (depicted on the top left panel as the increase in caliber of the red input in 'early' compared with 'late' stages of development with normal [Cl¯]i shift). Although these neurons can receive relatively large GABAergic synaptic input (blue), GABAA receptor activation typically depolarizes the membrane of young neurons because high [Cl¯]i, (green cloud), results in Cl_ efflux from the neuron when GABAA receptor channels open. Early glutamatergic input can result in calcium influx through NMDA receptors, or calcium-permeable a-amino-3-hydroxy-5- methyl-4-isoxazole propionic acid (AMPA) receptors. Depolarizing GABA responses can result in activation of voltage-sensitive calcium channels (purple). [Cl¯]i is high in young neurons because of the relative expression levels of the Cl¯ transporters NKCC1 (grey rectangle) and KCC2 (green rectangle). As excitatory glutamatergic drive increases with development, increased expression of KCC2 reduces [Cl¯]i so that GABAergic responses become hyperpolarizing. The top right panel depicts the consequences of premature expression of the Cl¯ transporter KCC2 at early stages of neuronal development. Even though NKCC1 is presumably still expressed under these conditions, this causes a premature reduction in [Cl¯]i (smaller green cloud). Xenopus optic tectal neurons in which [Cl¯]I was prematurely decreased within an otherwise normal visual system fail to increase the strength of glutamatergic input, as seen in normal neurons, but show significantly greater GABAergic input (larger blue triangles). The graph in the bottom panel shows that the ratio of AMPA:GABA inputs normally increases with development (between 4 and 16 days post-fertilization (dpf) in Xenopus optic tectal neurons), but is substantially reduced when neurons express KCC2 from relatively early stages of neuronal development. Expression of an inactive mutant form of the transporter does not affect the ratio of excitatory to inhibitory input. These data show that [Cl¯]I and depolarizing responses to GABA are a key determinant of the establishment of excitatory and inhibitory synaptic inputs *(Akerman and Cline, 2007).***

Previous studies demonstrate that maturation of glutamatergic synapses is required for the normal development of dendritic arbor structure. Blocking glutamatergic synapse development has been shown to impair the growth of dendritic arbors by reducing branch stabilization ***(Haas et al., 2006).*** This suggests that early depolarizing responses to GABA could be required for dendritic arbor development, and might influence dendrite development indirectly by interfering with glutamatergic synaptic maturation ***(Akerman & Cline, 2007).***

GABA depolarization might not necessarily increase excitation of neurons or the network, because the reversal potential of the GABAA receptor could be below action potential threshold and GABAA receptor activation can shunt other conductances ***(Lamsa et al., 2000).*** However, depolarization generated by GABAA receptors is well placed to facilitate local Ca2+ influx, where GABAergic depolarization can facilitate relief of the block of NMDA receptors. Cooperation with NMDA receptor activation represents an early form of coincidence detection between GABAergic and glutamatergic inputs. Indeed, the gradual developmental decrease in the $Cl^-$ reversal potential results in a systematic and significant decrease in the facilitation of the NMDA receptor conductance by GABAergic inputs ***(Akerman & Cline, 2006).*** NMDAreceptor activation is known to be crucial for proper dendritic development and synapse formation, and the degree of Ca2+ influx through

the NMDA receptor has been shown to dictate whether synapses are strengthened or weakened ***(Akerman & Cline, 2007).***

***GABA-ergic signaling during the refinement of developing neural circuits:***

Local feedforward and feedback GABAergic connections become established during the early period of synaptogenesis. Because these inputs impose temporal structure on activity patterns, whether GABAergic transmission is depolarizing or hyperpolarizing and when GABA conductances are active relative to other conductances could have important consequences for circuit activity and synaptic plasticity ***(Akerman & Cline, 2006).***

One hypothesis that emerges from these ideas is that during circuit development, the relatively depolarized reversal potential, combined with other aspects of the immature GABAergic system, sets a less stringent temporal rule for synaptic integration of excitatory synaptic inputs. This would provide a period during circuit development that would be more permissive for recognizing and strengthening convergent synaptic inputs, which could be essential for a cell to establish excitatory synaptic connections and become part of the network. This model predicts that depolarizing GABAergic synaptic activity is required for the development of neuronal circuits and that manipulations that interfere

with immature GABAergic signaling would result in abnormal circuit function ***(Akerman & Cline, 2007).***

***Balancing excitatory and inhibitory synaptic inputs during neural circuit development:***

An important requirement of circuit development is to maintain the balance of excitation and inhibition within a functional range. Intracellular $Cl^-$ is a key component in the delicate balance of excitation–inhibition during development, and alterations in $Cl^-$ transporter function have been shown to increase the susceptibility of the immature brain to unstable network activity and neonatal epilepsy ***(Dzhala et al., 2005).*** Both hyperpolarizing GABAergic inhibition and glutamatergic excitation are relatively weak during early development, and both increase as development progresses ***(Liu, 2004).*** There is relative overexpression of glutamate receptors during the first weeks of life. NMDA receptor density peeks in the neocortex and hippocampus at the end of the first week of life whereas maximal density of AMPA receptors appears during the second week. Kainate receptor density increases gradually over the first weeks of life ***(Mareš & Kubová, 2008).***

Studies in cultured neurons show that the balance of excitatory and inhibitory synaptic inputs can be homeostatically regulated. One explanation for this coordinated development is that inhibition is regulated to match the level of excitation. In other words, the

developmental increase in hyperpolarizing GABA transmission could be a response to changes in the glutamatergic excitatory drive, and not a director of circuit development. It is interesting; therefore, that several recent studies indicate that early depolarizing GABAergic transmission might be crucial for the coordination of subsequent levels of excitatory and inhibitory inputs ***(Akerman & Cline, 2007).*** Thus, complicated development of both systems together with developmental changes of GABA transporters may participate in age-specific effects of drugs ***(Mareš & Kubová, 2008).***

**Mechanisms of brain injury in epilepsy:**

Neuronal loss is the major neurobiologic abnormality in epileptogenic and epileptic brain. It is important that neuronal loss occurs together with other alterations, including gliosis, axonal and dendritic plasticity, neurogenesis and molecular reorganization of cell membranes and extracellular matrix ***(Artemowicz & Sobaniec, 2005).*** Other factors of neuronal cell loss include the uncoupling of local glucose utilization and blood flow, subsequent hypoxia, lactic acidosis, capillary endothelial damage and edema ***(Lee et al., 2001).***

Neuronal loss is the visible consequence of neurological insult and may occur via both necrosis and apoptosis. Cell death by necrosis can begin within minutes of injury, with alterations in intracellular ion flux, cellular swelling and

lysis. In contrast, apoptosis involves a complex cascade of events mediated by intracellular proteins and enzymes that produce programmed cell destruction in which the cell body shrinks and the nuclear material fragments. Apoptosis generally evolves over a longer period of time. It appears that necrotic mechanisms may activate apoptosis ***(Walker et al., 2002).***

***Excitotoxic cascade:***

Glutamate excitotoxicity is due to overstimulation of glutamate receptors producing excessive neuronal depolarization, which is accompanied by an overwhelming increase in free intracellular calcium, entering via glutamate receptor/channels and voltage gated calcium channels, as well as released from intracellular stores; the calcium-dependent signaling pathways that are subsequently activated lead to neuronal dysfunction (physiopathology), and/or pathology (alterations in morphology/ structure), or death ***(McNamara et al., 2006).***

High levels of intracellular calcium trigger calcium-dependent processes, such as the activation of proteases, lipid peroxidases and endonucleases and the production of oxygen free radicals, thereby destroying structural proteins, cell membranes and DNA ***(Weiss et al., 2000),*** osmolytic stress and cell swelling/rupture ***(Henshall, 2007).*** Intracellular accumulation of zinc may also play a critical role in seizure induced neuronal death ***(Weiss et al., 2000).***

Once begun, the excitotoxic cascade can propagate. The normal concentration of extracellular glutamate is about one thousandth that of the intracellular concentration, but reversal of glutamate uptake and the release of intracellular glutamate from dying cells can raise the ambient concentration around neighboring neurons to toxic concentrations ***(Walker et al., 2002).*** Furthermore, excitability and neuronal death can be modified by inflammatory mediators, such as the interleukins that are released during and following status epilepticus ***(De Simoni et al., 2000).***

***Apoptosis signaling pathways:***

Experiments in the mid-1990s identified DNA fragmentation patterns in seizure-damaged brain that were known to be a biochemical hallmark of apoptosis. Apoptosis is a morphologically distinct form of cell death characterized by cytoplasmic condensation, preservation and packaging of intracellular organelles, DNA fragmentation, dispersal and phagocytosis of the cell as apoptotic bodies. Apoptosis signaling pathways are typically initiated following perturbation of intracellular organelle function (intrinsic pathway) or by activated cell-surface-expressed death receptors (extrinsic pathway) ***(Henshall, 2007).***

Seizures cause mitochondrial dysfunction and activate intrinsic pathway components including pro-apoptotic Bcl-2 family proteins and caspases, processes that may be partly

calcium-induced. The ER (endoplasmic reticulum) has emerged as a major intrinsic pathway trigger for apoptosis and its function may also be compromised following seizures and in epilepsy. The extrinsic, death receptor-dependent pathway is also rapidly engaged following experimental seizures and in patient brain, supporting a previously unexpected apical role for a calcium-independent pathway. When considered alongside emerging functions of apoptosis-regulatory proteins in non-cell-death processes, including regulating intracellular calcium release and neuronal (re)structuring ***(Henshall, 2007).***

Studies on temporal lobe material surgically obtained from patients with intractable epilepsy. However, the extent to which these pathways culminate in cell death in patient brain is still at issue because few cells exhibit end-stage DNA fragmentation in such specimens, suggesting concurrent anti-apoptotic processes may also be engaged ***(Henshall, 2007).***

**Epileptogenic role of astrocyte dysfunction:**

Alterations in astrocyte function, often associated with reactive astrogliosis, are described in epilepsy using both experimental models and human tissue resected at surgery. The repertoire of gliotransmitters that mediate the functional communication between astrocytes and neurons as well as the ability of astrocytes to affect neuronal excitability (for example, by regulating the clearance of extracellular K+ and glutamate) are the basis for studying whether and to what

extent specific defects in astrocyte function and signaling may contribute to neuronal network hyperexcitability underlying seizures ***(Volterra & Meldolesi, 2005).*** In this context, recent evidence has shown that reactive astrocytes represent a chronic source of inflammatory mediators in human and experimental epileptic brain tissue and that some of these mediators, such as IL-1β, have a proconvulsant action and can contribute to neuronal cell loss ***(Ravizza et al., 2008).***

Studies in rodent models of seizures and epilepsy have reported astrocyte loss in the hippocampus following status epilepticus and subsequent newly generated astrocytes with altered functional properties. Astrocyte loss preceded and was strictly associated with neuronal cell degeneration in the hilus of the hippocampus. These studies suggest that astrocytic cell loss is a consequence of epileptic activity ***(Vezzani, 2008).***

Astrocytes could play an important pathophysiological role since their dysfunction or loss in them may compromise energy metabolisms, K+ homeostasis, or GABA and glutamate catabolism and reuptake. Moreover, activated astrocytes may release excitotoxic amounts of glutamate, proinflammatory cytokines, and reduce the availability of adenosine (a brain metabolite endowed with anticonvulsant activity) via endogenous upregulation of adenosine kinase. These changes in astrocytic cell function, stemming from their pathological activation or apoptotic loss, potentially

could contribute to the acquisition of the properties of the epileptic tissue. Further elucidation of these novel aspects may offer a new perspective into the mechanisms of epileptogenesis in other types of epilepsies ***(Vezzani, 2008).***

**Haemodynamic changes during epileptic seizures:**

Cerebral blood flow velocity (CBF) and cerebral energy metabolism are normally closely related to local neuronal activity, which includes the neuronal firing rate and field potentials from synaptic activity of neurons. However, very little is known about the coupling of neuronal activity and CBF under abnormal conditions, such as epileptic seizures ***(Nersesyan et al., 2004).***

It has long been known, based on observations of the exposed human cerebral cortex during surgery, that epileptic seizures are associated with macroscopic increases in cerebral perfusion. However, subsequent investigations have yielded contradictory results in different seizure types, particularly with regard to absence. Human and animal studies have shown large increases in neuronal activity, CBF, and metabolism during GTCS ***(Nersesyan et al., 2004).***

Recent advances in neuroimaging such as PET, single photon emission computed tomography (SPECT), have improved seizure focus localization and understanding of the pathophysiology of epileptic foci. Ictal SPECT and PET show

changes in CBF and metabolism during seizures ***(Haginoya et al., 2001).***

During epileptic seizures there is high frequency neuronal firing in the cerebral cortex causing massive synchronized activity in both presynaptic and postsynaptic local microcircuits ***(Nersesyan et al., 2004).*** Different types of seizures may interfere with normal information flow in the brain via different mechanisms, with some seizures producing greater and others less neuronal activity, either of which may disrupt normal processing ***(Blumenfeld & Taylor, 2003).***

Therefore, unlike convulsive seizures during which CBF and metabolism widely increase, our data are in favor of a normal or decreased ictal metabolism and of increased interictal glucose utilization in the brain with absence seizures ***(Nehlig et al., 1996).***

Regional CBF (rCBF) and metabolism increase in the epileptogenic zone during partial seizures, but decrease interictally. However, ictal hypo-perfusion of the epileptogenic zone has also been reported in some cases using SPECT ***(Haginoya et al., 2002).***

Focal seizures elicit an increase in rCBF in the seizure focus by decreasing cerebrovascular resistance, which is mediated by local tissue changes, such as changes in nitric oxide, Ph and $CO_2$ and adenosine. However, the propagation

of seizure activity to subcortical systems induces mass excitation of the sympatho-adrenal axis and brain stem centers affecting autoregulation, resulting in remarkable change in CBF ***(Haginoya et al., 2002).***

Several pathophysiological processes exist during epileptic seizures in childhood:

- Convulsive seizures were associated with a remarkable increase in CBV, while absence seizures were associated with mild decrease or no change in the CBV of the frontal cortex.
- Initial transient decrease in CBV and deoxygenated Hb were observed in some types of convulsive seizures.
- An ictal increase in CBV changed to an ictal decrease in the course of tonic status epilepticus.
- There was definite heterogeneity in the CBV changes during tonic spasms in patients with West syndrome ***(Haginoya et al., 2002).***

**Cerebral damage in epilepsy:**

Early views maintained that seizures damaged the brain and that children with epilepsy suffered potentially severe consequences as a result of having epilepsy ***(Berg et al., 2004).*** There are several clinical differences between seizures in the immature brain as compared to those in adult brain. Neonates and infants are more susceptible to seizures than adults, and have different seizure characteristics and responses to AED. Also, certain types of seizures in early life,

such as febrile seizures, are associated with increased likelihood of chronic epilepsy later in life and may themselves contribute to epileptogenesis (the transformation of the brain to a long-lasting state in which recurrent, spontaneous seizures occur) ***(Acharya, 2002).*** Seizures can act on this epileptogenic substrate, causing additional structural and functional changes ***(Walker et al., 2002).***

Many data support the idea that prolonged or frequent seizures in young animals and patients lead to later cognitive deficits, which can often be subtle. In both laboratory animals and humans, the brain's susceptibility to seizures is increased during specific developmental periods, yet the behavioral consequences of seizures tend to have clearly complex relations with the age of onset and it is not fully understood ***(Sayin et al., 2004).***

Seizure during early brain development can result in life-long behavioral and cognitive deficits, with significant learning and memory deficits and persistent anxiety in adulthood. The lack of major hippocampal structural damage in some studies suggests that seizures early in life can have long-term cognitive consequences despite the absence of overt cellular damage. These results suggest that seizures disrupt some aspect of hippocampal function during the early, vulnerable critical period of brain development ***(Sayin et al., 2004).***

These changes were thought to be related to the loss of plasticity caused by the excessive neuronal activity of seizure. Therefore the dentate gyrus appears to be a site of long-term cellular alterations induced by abnormal patterns of postnatal neural activity. It is likely that other hippocampal and extrahippocampal areas also are involved in these maladaptive plastic changes after early life seizures ***(Sayin et al., 2004).***

Such damage occurs even before the full maturation of hippocampal circuits, it is apparent that subsequent developmental events are not sufficient to overcome the adverse effects of early postnatal seizures. As substantial evidence indicates that status epilepticus in the developing brain does not produce the overt macroscopic damage seen in adults, the observation of long-term behavioral and memory deficits in many studies support the view that the term seizure-induced damage also should include adverse functional consequences ***(Sayin et al., 2004).***

Seizures induce alteration of synaptic plasticity, so, chronic behavioral effects of early seizures on hippocampal-based memory demonstrate the influence of activity-dependant and seizure-induced plasticity during development on subsequent cognitive function in adulthood. These findings suggest that seizures early in development are not as harmless as was once thought ***(Sayin et al., 2004).***

Despite the prevalence of widespread structural abnormalities in patients with chronic epilepsy, the timing and pathogenesis of such changes remain obscure ***(Liu et al., 2005).*** Three long-continuing questions still prevail in the field of epilepsy pathology: first, how and when neuronal loss occurs; secondly, whether all types of neurons are equally affected; and thirdly, whether this loss is secondary to epileptic seizures or represents a primary process which initiates the development of seizure activity ***(DeFelipe, 1999).*** The crucial question relates to whether the abnormalities are progressive and the cumulative effect of years of epilepsy; the effect of an initial precipitating insult during a vulnerable phase of cerebral development; the presence of a preexisting developmental abnormality predisposing to insults and further cerebral damage; or a combination of these factors acting synergistically (***Liu et al.,2005).***

To investigate the long-term consequences of epilepsy early in life, several animal models have been developed. Most of these models use chemo-convulsants to induce acute seizures, mimicking status epilepticus. Later, a variety if tests assessing behavioral and cognitive function, seizure susceptibility, and histologic evidence of neuronal damage are applied. For example, kianic acid which is an epileptogenis substance (KA) has been used to investigate the behavioral consequences of status epilepticus at various ages. It was found that seizure induced behavioral impairments may occur in later life in response to status epilepticus

during early development ***(Sayin et al., 2004).*** Childhood-onset epilepsy has been shown to have long-term adverse effects persisting into adulthood, even among persons whose seizures are in remission ***(Strine et al., 2005).***

When status epilepticus was established, the pyramidal neuron numbers were significantly reduced. This implies that a severe seizure activity is necessary to induce characteristic neuron loss in this model of epilepsy. These findings are consistent with quantitative studies performed in rats and in humans ***(Gulec & Noyan, 2000).*** In vitro models of status epilepticus have shown that epileptogenesis can be progressive even after the epileptogenic agent or stimulus is withdrawn and that cell loss can occur acutely, possibly as a result of seizures ***(Acharya, 2002).***

Depending on the method of seizure induction, dose, age of administration, and behavioral testing, investigators have found varied effects of early seizures on subsequent learning and behavior. They recently provided additional evidence for long-term adverse cognitive changes after KA-induced status epilepticus in early development. KA seizures were evoked during early postnatal development; it was associated with life-long impairment in spatial learning and memory ***(Sayin et al., 2004).***

## Partial (focal) seizures:

### *Normal hippocampal anatomy and structural reorganization in epilepsy:*

The hippocampus consists of the Cornu Ammonis subfields CA1 through CA4 and the dentate gyrus. The primary neurons of the Cornu Ammonis are the pyramidal cells while those of the dentate gyrus are granule cells. The axons of granule cells are called mossy fibers and these are normally not seen in the inner molecular (supragranular) layer where the dendrites of granule cells are present. The hippocampal circuitry consists of a trisynaptic excitatory pathway –from the entorhinal cortex to the dentate granule cells, which project to the CA3 pyramidal neurons via mossy fibers, and from there to the CA1 region through collaterals. There are local circuits in each region with excitatory and inhibitory interneurones. The CA3 region is most prone to epileptiform activity, partly because of excitatory connections with neighboring cells. On the other hand, it is difficult to induce seizures in granule cells, in part due to the lack of excitatory connections with neighboring granule cells and the presence of strong polysynaptic inhibitory synapses on granule cells. Normally, dentate granule cells limit seizure propagation through the hippocampal network. However, structural reorganization with alteration of the synaptic circuitry may transform the granule cells into an epileptogenic population and promote seizure initiation and/or propagation ***(Acharya, 2002).***

The mossy fiber sprouting (MFS) hypothesis refers to the synaptic reorganization of the mossy fiber axons of the granule cells *(Figure 2)* so that they project into the inner molecular layer of the dentate gyrus and make excitatory contact with granule cell dendrites, resulting in a recurrent excitatory circuit which eventually leads to seizures. The explanation offered for the fact that spontaneous seizures occur only intermittently, despite a fixed structural change, is that intact synaptic inhibition normally suppresses the effect of the excitatory circuit. Seizures occur only when inhibition is transiently decreased ***(Acharya, 2002).***

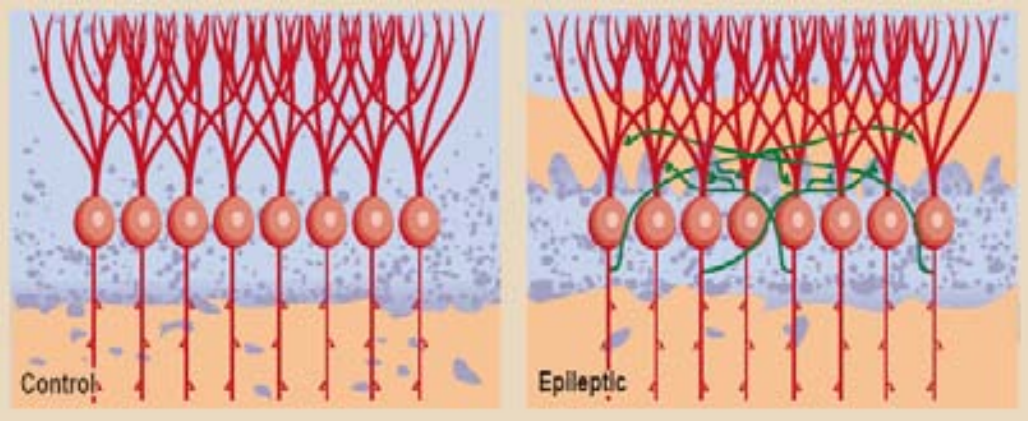



**Figure (2): Recurrent excitatory networks may be formed by reorganized mossy fibres. Schematic representation of dentate granule cells superimposed on the dentate gyrus of a control (left) and kainite treated (right) epileptic rat. Timm stain (denoted by light brown colouring) reveals the mossy fibres in the hilus of both animals but in the inner molecular layer of the dentate gyrus only in the epileptic rat. The granule-cell bodies and their dendritic trees are evident in both the control and the epileptic rat, but the sprouted mossyfibre axons are only in the epileptic rat and overlay the Timm stain in the molecular layer; these schematized sprouted axons reflect the putative recurrent excitatory networks formed among the granule cells *(McNamara, 1999).***

The precise stimulus that causes MFS is not known. Because MFS is typically seen in a sclerotic hippocampus with extensive neuronal loss, it has generally been believed that death of susceptible neurons such as the mossy cells, which normally project to the inner molecular layer, is the initiating stimulus. Axons of the surviving neurons then fill up the vacated synapses. Further, seizures themselves may kill the susceptible neurons and set up a vicious cycle – seizures cause neuronal death, which leads to MFS, which in turn leads to more seizures. Many studies have shown that seizure activity alone, if sufficiently prolonged or vigorous such as status epilepticus, causes death of vulnerable neurons. A recent study suggests that brief, repeated seizures also can cause neuronal death ***(Acharya, 2002).***

Of the partial epilepsies, temporal lobe epilepsy (TLE) has been extensively studied with respect to mechanisms of epileptogenesis in the last decade ***(Acharya, 2002).*** Chronic intractable epilepsy is associated with significant structural alterations both within and beyond the epileptogenic zone ***(Liu et al., 2005).***

Temporal lobe epilepsy (TLE) is a common neurological disorder which is frequently drug-resistant. A number of studies have focused on the pathophysiological mechanisms underlying this disease. The common neuropathological lesion is hippocampal sclerosis, characterized by neuronal loss and gliosis in the hippocampus. It has been reported that a severe convulsion

in early childhood may be responsible for the characteristic neuronal loss in hippocampal sclerosis. The most vulnerable neurons in the hippocampus are CA1 and CA3 pyramidal cells and dentate hilar neurons ***(Gulec & Noyan, 2000),*** CA4, and the subiculum ***(Kanner, 2005)***, whereas CA2 neurons and dentate gyrus granule cells are relatively resistant ***(Gulec & Noyan, 2000).*** In mesial temporal sclerosis, neuropathologic findings consist of, in addition to neuronal cell loss, astrocytosis in hippocampal formation, amygdala, entorhinal cortex, and occasionally in parahippocampal gyrus ***(Kanner, 2005).***

Animal models develop bilateral neuronal loss not only in the limbic areas including the hippocampus and amygdala, but also in extralimbic regions such as thalamus, hypothalamus, and certain areas of the cerebral cortex ***(Sharma et al., 2007).***

Intractable TLE also may be associated with extralesional volume deficits, including the ipsilateral and contralateral temporal lobe; contralateral hippocampus; ipsilateral amygdala, entorhinal and perirhinal cortex, thalamus and caudate, and cingulate gyrus. Cross sectional magnetic resonance imaging (MRI) studies of patients with intractable epilepsy also have reported significant cerebellar and cerebral volume reduction ***(Liu et al., 2005).***

Cross-sectional studies have shown significant ipsilateral hippocampal volume reduction in patients with

frequent seizures and prolonged duration of TLE. It has thus been proposed that volume reductions reflect either (a) the cumulative neurobiologic effect of repeated seizures or (b) a bias toward the accumulation of refractory cases after a severe precipitating injury. Some study confirmed that patients with TLE had significantly reduced hippocampal volumes at baseline ***(Liu et al., 2005).***

Some studies have shown that TLE is associated with the development of subtle neocortical atrophy. Temporal lobe atrophy was observed in 17% of patients with chronic TLE and HS, suggesting that neuronal damage may extend beyond the hippocampus to involve the ipsilateral temporal lobe, particularly in the presence of severe hippocampal damage from an initial brain injury ***(Liu et al., 2005).***

**Generalized epilepsy:**

Regarding generalized epilepsy studies, especially absence epilepsy have been made only in the last decade ***(Acharya, 2002).*** Childhood absence epilepsy (CAE) is a subsyndrome of idiopathic generalized epilepsy (IGE) ***(Chan et al., 2006).***

From both animal and human data, it appears that the 3 Hz generalized spike and wave pattern results from a perturbation of a physiological, higher frequency thalamocortical oscillatory rhythm. Thalamocortical rhythms form the substrate of the neurobiology of sleep, and the

mechanisms underlying sleep spindles and the generalized spike and wave EEG pattern may be related. Because sleep spindles originate in the thalamus, it appears to be the pacemaker in absence seizures but the participation of the cortex is essential, and an intact thalamocortical loop is necessary for the full expression of absence seizures. However, in humans what precise aberration of the thalamocortical circuit occurs in absence seizures is not known ***(Acharya, 2002).***

IGE patients have no abnormalities on visual inspection of their MR images. Previous volumetric studies suggested the presence of increased cortical grey matter (GM) volumes in patients with various IGE subsyndromes. The volume of subcortical may decrease as well ***(Woermann et al., 1998).***

Chan et al. using voxel-based morphometry (VBM) study on patients with CAE documented GM volume reduction bilaterally in the thalamus, as well as in the subcallosal gyrus of the frontal lobe. Additionally, CAE patients showed white matter (WM) volume reduction in the frontal lobe and cingulate, as well as extensive WM changes in the sublobar region. In contrast, only weak evidence was seen for any regional increase in GM or WM in these CAE patients ***(Chan et al., 2006).***

There study demonstrated GM deficits in the thalamus, particularly in the right and left dorsomedial nucleus. The

important role of the thalamus in IGE has been documented in animals and in electrophysiological studies on humans. Functional involvement of the thalamus in human absence epilepsy also has been suggested by using positron emission tomography (PET) and functional MRI during absence seizures or with interictal discharges ***(Chan et al., 2006).***

There results of the GM and WM analysis in IGE demonstrate that some regions show both GM and WM atrophy (e.g., region of basal forebrain), whereas others show an isolated change in one tissue class (e.g., temporal lobe WM). Finally, in some areas, an increase in one tissue is mirrored by a decrease in the other tissue (e.g., right pallidum) ***(Chan et al., 2006).***

Volume reduction, affecting both WM and GM areas, was found in the basal frontal lobe. Recent animal and electrophysiological studies have demonstrated that the basal forebrain cholinergic system is important in the sleep–wake cycle ***(Amzica, 2002).*** Therefore an alteration of the cholinergic input via the basal forebrain may promote a dysregulation of the thalamic oscillations. Further areas of GM and WM volume reduction were in the anterior and posterior cingulate and retrosplenial areas. An involvement of the cingulate and retrosplenial areas in IGE has been suggested in *f*MRI/EEG studies ***(Archer et al., 2003).*** The prominent deactivation of the posterior cingulate, associated with interictal discharges, was interpreted as reflecting a

state of reduced awareness, as observed during the absence seizures. These areas of WM decrease encompass WM tracts terminating and originating in the thalamus, and their reduction may reflect a partial degeneration in relation to the thalamic atrophy. These findings add further support to the central role of thalamocortical circuits in the generation of generalized spike-and-wave discharges in CAE ***(Chan et al., 2006).***

Cerebellar atrophy in epilepsy has previously been considered a consequence of either prolonged phynetoin therapy, seizure-mediated cellular damage through cerebrocerebellar diaschisis, hypoxic damage, or status epilepticus ***(Liu et al., 2005).***

**The role of GABAergic interneurons in epilepsy & behavioral changes:**

Experimental and clinical data suggest that epilepsy is caused by an imbalance between excitatory and inhibitory neurochemical systems in the brain and that gamma-aminobutyric acid (GABAergic) interneurons play a critical role in maintaining this balance. By acting as a sensory gate, inhibitory GABAergic interneurons regulate the degree of glutaminergic excitation in the neocortex, filtering the input, and coordinating the output of multiple projection neurons. The fact that an approximate 6:1 ratio of glutamatergic neurons to GABAergic interneurons in the neocortex is consistently observed across mammalian species suggests

that this ratio may represent an important numerical balance for normal brain function and behavior. GABAergic interneurons comprise only a small subfraction of cells in the neocortex. Nonetheless, disruption of their development, and hence the delicate balance between excitation and inhibition, may have profound neuropsychiatric repercussions ***(Levitt et al., 2004).***

Chandelier cell, which is considered to be the most powerful cortical GABAergic inhibitory interneuron, is probably a key component of cortical circuits in the establishment of human intractable temporal lobe epilepsy. These cells (among other types) have been found to be lost or reduced at epileptic foci in both experimental animals and epileptic patients. A hypothesis is presented by which the normal variability in the number of interneurons might explain the predisposition of some individuals to develop epilepsy more than others as a result of a lesion or other precipitating factors that lead to loss of neurons. The sources of GABAergic input on dendrites and somata of cortical pyramidal cells originate from many and diverse types of interneurons but, at the level of the axon initial segment of these cells, all synapses come from a few chandelier cells. Loss of one class of interneurons ending on soma and dendrites might have relatively little impact on the inhibitory control of the pyramidal cell. However, if chandelier cells were affected, it would have serious consequences for the inhibitory control of the pyramidal cells ***(DeFelipe, 1999).***

There is also evidence suggesting that different types of GABAergic interneurons in the amygdala may have different susceptibilities to seizure-induced damage. What makes certain types of interneurons more vulnerable to seizures and what the implications of such differential sensitivities are on the excitability of the amygdala circuitry remain to be determined ***(Aroniadou-Anderjaska et al., 2008).***

The molecular cues that guide the movement of interneurons at each decision point are not well understood. Convergent evidence suggests that multiple cues are involved, including repulsive/attractive cues that force cells to change their course of direction during migration and growth factors, such as brain-derived neurotrophic factor (BDNF), neurotrophin 4 (NT4), and Hepatocyte growth factor/scatter factor (HGF/SF), which induce the motility of cells ***(Marin et al., 2003).***

The increased susceptibility of mutant mice to seizures is consistent with a 50% decrease in cortical GABAergic interneurons and diminished inhibitory control of excitatory neurotransmitter systems. The fact that mutant mice also show an increased sensitivity to low dose diazepam (0.1–1.5 mg/kg), as indicated by a dose-dependent reduction in locomotor activity, suggests that there may be simultaneous changes in the number and/or sensitivity of benzodiazepine receptors to compensate for the loss of GABAergic tone ***(Levitt, 2005).***

Studying the behavioral consequences of developmental perturbations in the maturation of GABAergic interneurons, it was found that mutant mice consistently display behaviors indicative of increased anxiety. Mutant mice are presented with a conflict between their natural drive to explore novel places and their fear of open or brightly lit spaces. With time, normal mice will overcome their fear and begin to explore the open spaces. Failure to explore or reduced exploratory activity relative to normal controls is interpreted as increased anxiety ***(Powell et al., 2003).***

In addition to increased anxiety, mutant mice also exhibit impaired social behavior, in the resident-intruder task; an unfamiliar (intruder) mouse is introduced into the home cage of another mouse. The pair of mice is then observed for a designated period of time to assess the degree and type of social interaction ***(Levitt, 2005).***

A single mutation of the gene that regulates the direction of migration of the GABAergic neurons, results in a constellation of permanent neuroanatomical, neurochemical, and behavioral defects. The presence of these defects underscores the importance of the GABAergic interneuron circuitry in the maintenance of normal behavior and the challenge presented to the developing brain to override such specific defects through adaptation. The consequences of this neuropathology are, in turn, reflected in a number of

concomitant behavioral deficits, including an increased susceptibility to seizures, heightened anxiety in novel situations, and impaired social behavior. These findings are consistent with the interpretation that early disruption of GABAergic interneuron development results in diminished inhibitory control of cortical excitatory neurocircuitry and an abnormal formation of cortical maps ***(Levitt, 2005).***

# ***Psychiatric co-morbidity in children with epilepsy***

Children with epilepsy have high rates of co-morbid psychiatric disorders ***(Leonard & George, 1999)***; they are often under-diagnosed and under-treated for psychiatric disorders. Perhaps because the immediate responsibility of coping with seizures and their consequences is overwhelming, families may not associate a child's emotional and behavioral functioning with epilepsy, and so may not bring it to the physician's attention. Additionally, physicians may overlook the psychiatric symptoms as they are confronted with the challenges in attaining maximal seizure control ***(Plioplys, 2003a).***

The high prevalence of mental health problems in children with epilepsy (CWE) has not changed over the past 30 years, despite remarkable progress in timely diagnosis, effective treatment, and positive long-term seizure outcome. During the past decade, several population-based studies of patients with childhood-onset epilepsy reported poor psychosocial outcome in adulthood even for patients who had full seizure remission and were no longer taking antiepileptic drugs. These studies identified lower levels of education, employment, marriage, and fertility. Mental retardation and learning problems were the stronger predictors of poor psychosocial outcomes in adulthood ***(Plioplys et al., 2007).***

Just as epilepsy is a heterogeneous disorder with multiple etiologies, seizure types and syndromes, and variable degrees of seizure control, there are multiple factors that influence the risk of psychopathology in children with epilepsy. Factors to be considered in assessing the prevalence of behavioral problems include demographic variables, neurological variables, seizure variables, therapy, and psychosocial variables ***(Dunn & Austin, 2004).***

Theoretical models of psychopathology propose that psychopathology stems from complex interactions between multiple etiological variables. Extensive research has been conducted investigating risk factors *(Table 3)* for psychopathology in CWE. However, difficulty separating the effects of the risk factors in cross-sectional studies with small sample sizes has often produced inconsistent findings. Recent studies provide evidence for the moderating and mediating effects of family-related risk factors on the development of psychopathology in CWE ***(Plioplys et al., 2007).***

***Risk factors:***
***General:***

Demographic variables have been minimally predictive of the likelihood of psychiatric or behavioral problems. Gender is inconsistent as a predictor of problems. Age at onset of seizures is more predictive of cognitive problems

than of behavioral difficulties. Lower socioeconomic status, defined by either income or caregiver education, has been associated with behavioral problems ***(Dunn & Austin, 2004).***

**Table (3): Risk factors for behavioral problems in pediatric epilepsy:**

| | |
|---|---|
| ***General risk factors*** | ***Demographic variables***<br>• Age<br>• Gender<br>• Socioeconomic status<br><br>***Neurological variables***<br>• Additional central nervous system dysfunction<br>• Mental handicap<br>• Severe epileptic syndromes<br>• Intractable epilepsy<br>• Early age of seizure onset<br>• AED polytherapy |
| ***Family & child factors*** | ***Psychosocial variables***<br>• Family stress and mastery<br>• Child response to illness<br>• Stigma |

A more definite risk factor for behavioral problems is the presence of additional central nervous system damage. Seizure variables have been associated with behavioral problems in children with epilepsy. Seizure type has been inconsistent as a predictor. Seizure syndrome is probably a

more important factor. The children with catastrophic epilepsies such as West syndrome or Lennox–Gastaut syndrome have more behavioral and cognitive troubles. Seizure severity and seizure frequency are important variables in predicting behavioral problems. Moreover, even in children with new-onset seizures, recurrent seizures were a predictor of behavioral problems. Behavioral problems in this patient population are also associated with some antiepileptic drugs (AEDs) ***(Dunn & Austin, 2004).***

***Family and child factors:***

Family factors also influence the incidence of behavioral problems. The families who are able to deal with the child's epilepsy, who feel confident that they can handle the problems associated with pediatric epilepsy, are the ones who are able to transfer this confidence to their children, resulting in a better quality of life ***(Dunn & Austin, 2004).***

The child's own response to his or her epilepsy is also significantly associated with behavioral problems. McNelis et al. study found that children and adolescents worry about their epilepsy and the social impact it has on their lives. Some of them worry about dying and, specifically, about dying from their seizures. It is important to identify these children ***(McNelis et al., 1998).*** Overall, children who have a negative attitude toward their illness develop more problems related to self-concept, and are more likely to develop depression ***(Dunn & Austin, 1999).*** There are studies showing that

children and families who have had problems before the seizures started were more prone to develop behavioral problems after seizure onset ***(Oostrom et al., 2003).***

To conclude, general risk factors, such as the child's age, sex, and socioeconomic status have not been consistently associated with psychopathology in CWE. However, the child's cognitive functioning and family risk factors have been consistently associated with psychopathology in CWE ***(Plioplys et al., 2007).*** Several researchers have concluded that seizure frequency has a different effect on psychopathology in cognitively normal children compared with children with symptomatic epilepsy, epileptic encephalopathies, and mental retardation ***(Berg et al., 2004).***

Although cognitive and family variables are consistent risk factors for mental health problems in CWE, the debate continues regarding the possible role of epilepsy-related variables in the psychopathology of cognitively normal children with idiopathic epilepsy. The majority of studies have found no association among age at onset, seizure frequency, seizure type, lateralization of seizure focus, and psychopathology in CWE ***(Caplan et al., 2004).*** New findings on a large sample of children with childhood absence epilepsy and average intelligence imply a role for seizure variables ***(Siddarth et al., 2006).***

Typically, it is assumed that the relationship between psychiatric and seizure disorders is one in which psychiatric co-morbidities are a complication of the seizure disorder and/or of the underlying neurological insult that caused the epilepsy ***(Kanner, 2008).*** CWE have a broad spectrum of psychopathology, but attention, internalizing problems, and thought problems may be relatively specific to epilepsy ***(Rodenburg et al., 2005a).*** A variety of co-morbid psychiatric disorders have been reported among persons with epilepsy, including anxiety, attention deficit disorder, bipolar disorder, and psychosis, although depression is the most prevalent ***(Strine et al., 2005).***

Epilepsy is associated with focal or regional cerebral abnormalities. Though local, these may impair functions at a distance and they can create a deleterious effect on the functional organization of the brain. Impairment of cerebral function may also impair the individual's ordinary mechanisms of psychological defense. These mechanisms, such as denial or projection, are the means by which an individual copes with the world ***(Raguraman & Wadoo, 2006).***

Previous study found a 27% incidence of psychopathology in epileptic school children, compared to 15% in controls. From 10 to over 50% of children with seizures are reported to have psychopathology affecting learning, behavior and conduct. There is considerable

heterogeneity in psychopathology of children with epilepsy ***(Leonard & George, 1999).***

In a previous study, the researchers noted that 30% of epileptic children had psychiatric disorders compared with 6.8% of children in the general population. Additionally, children who had complicated epilepsy were more likely to have psychopathology. In attempting to identify causes for psychiatric disturbance, the authors found that psychiatric disturbance did not correlate with seizure frequency, age of onset, visibility of handicap or social prejudice. However, there was a positive correlation with lower IQs, complex partial seizures, demonstrable brain lesions, marital discord, family disruption and adverse effects of anticonvulsants ***(Rutter et al., 1976).***

Some studies suggested that the prevalence of psychiatric disorders is two to four times greater among epileptic children, and raised the possibility that children with complex partial seizures exhibit greater psychopathology. Hoare (1984) compared children with chronic and newly diagnosed epilepsy, children with chronic and newly diagnosed diabetes and normal healthy children. Children with epilepsy had a higher rate of psychiatric disturbance, but there were no differences in prevalence between children with newly diagnosed and chronic epilepsy ***(Leonard & George, 1999).***

Children with epilepsy may be psychiatrically disturbed at the onset of seizures which may be related to brain dysfunction ***(Leonard & George, 1999).*** This finding of higher rates of behavior problems at seizure onset in children who were having unrecognized seizures is consistent with Aicardi's proposal that epilepsy can be a pervasive condition in which the manifestations include seizures as well as behavioral disturbances. One may reasonably ask what the nature of the mechanism is that might be related to both seizures and behavioral disturbances. Aicardi proposes that transient cognitive impairment (TCI) caused by subclinical epileptiform discharges might be this mechanism because TCI can lead to disorganization and suppression of normal brain functioning. One could argue that children with previous seizures would be more likely to have subclinical epileptiform discharges than children without previous seizures ***(Austin et al., 2001).***

Support for this hypothesis includes the empirical evidence that epileptiform discharges that are not accompanied by clinically observable seizures may result in brief episodes of impaired cognitive functioning and reduced psychosocial functioning. It has been hypothesizes that episodes of TCI can adversely affect interpersonal interactions or social functioning if it should cause the child to miss important social or emotional cues during interactions with peers, or whether the child experienced interruptions in the flow of conversations, leading to failure

to respond appropriately ***(Austin et al., 2001).*** The authors of another paper suggest that behavioral aggression may result from certain abnormal regions of the brain producing epileptic activity or may be aggravated by the effects of antiepileptic drug therapy ***(Elliot et al., 2004).***

Some of the most common emotional and behavioral difficulties seen in these children include increased anxiety, depression, irritability, hyperactivity, aggression, and in some cases, irrational periods of rage. In a more recent study of behavior in children in the 6 months before a first recognized seizure, 24.6 % of the children had higher than expected rates of behavioral problems (particularly attention difficulties). This finding suggests that epilepsy is a more complex disorder that may manifest itself with behavioral disturbances, as well as seizures ***(Elliot et al., 2004).***

Vulnerable periods for the development and course of psychopathology in CWE have not been systematically investigated. New data have become available on psychopathology in children with new-onset epilepsy, which is a unique subgroup of CWE from clinical and research perspectives. Due to a recent onset of epilepsy, these patients are not yet exposed to the effects of the AEDs, long-term impact of epileptic activity on brain development, and the burden of living with chronic illness. Interestingly, both epilepsy-related and preexisting family variables correlated significantly with behavioral problems in children with new-onset epilepsy ***(Austin et al., 2001).***

A 3.5 year-long prospective study reported more behavioral difficulties in children with new-onset idiopathic epilepsy compared with healthy controls both at baseline and over time. At baseline, up to 25% of CWE compared with 6% of controls had CBCL total behavioral problems in the clinical range. During the 3.5 years follow-up, 22% of CWE had behavioral problems compared with 6% of controls. The overall rates of psychopathology in this clinical sample had not changed over the 3.5 years, but the individual children with psychopathology had changed over time. This finding suggests that behavioral problems were not persistent in the same individual children over time. Preexisting and ongoing family problems and parenting difficulties rather than seizure-related variables strongly predicted behavior problems both at the onset of epilepsy and at follow-up ***(Oostrom et al., 2005).***

Yet, the negative impact of psychiatric disorders at the time of epilepsy onset is not restricted to potential risks of future psychosocial maladjustments; it also may herald a worse response to treatment with antiepileptic drugs. Indeed, in a study of 780 patients with new-onset epilepsy, it was found that those with a history of psychiatric disorders, detected at the time of diagnosis of the seizure disorder, were almost 2.5 times more likely to develop refractory epilepsy. The evaluation of patients with epilepsy cannot be restricted to seizure-related data but must include a careful

investigation of previous psychiatric and cognitive disturbances even in patients with new-onset epilepsy ***(Kanner, 2008).***

Complex partial seizures (CPS) are common in the pediatric population and affected children appear to be at increased risk for cognitive, academic, behavioral, and psychosocial difficulties. CPS represent a localization-related form of epilepsy, usually involving the temporal lobe(s) Therefore, it is not surprising that memory impairments have been reported frequently in both adult and pediatric populations. In addition to the increased risk for cognitive impairment, children with CPS have more behavioral problems and difficulties in social–emotional adjustment ***(Schoenfeld et al., 1999).***

Community studies of children with complex partial seizures (CPS) who have average IQ rather than seizure variables predict the presence of a psychiatric diagnosis ***(Caplan et al., 2004).*** Increased CBCL externalizing ***(Caplan et al., 2006)***; and internalizing scores ***(Schoenfeld et al., 1999)***, disruptive disorder diagnoses, poor peer interactions, and academic underachievement were strongly associated with impaired use of language to formulate and organize thoughts in children with CPS ***(Caplan et al., 2006).*** These findings suggest that cognitive and linguistic co-morbidities, like psychopathology, are integral components of CPS ***(Plioplys et al., 2007).***

In short, children with focal seizures appear to be particularly vulnerable to mental health problems but it is not clear whether temporal lobe epilepsy is related to an even higher risk of psychopathology. Overall, very little is known about whether specific underlying causes of epilepsy, or localization of the CNS pathology, predispose individuals to increased risk of particular types of psychopathology ***(McLellan et al., 2005).***

Despite the adverse effects of psychiatric disorders on persons with seizure disorder or epilepsy, these conditions are under-recognized and under-treated in this population. Many studies suggest that it is advisable for healthcare professionals to screen for psychiatric and physical co-morbidities among patients with a history of seizures to improve patient health outcomes ***(Strine et al., 2005).***

***ADHD and Disruptive disorders:***

Behavioral neurology has been bridging the gap between neurology and psychiatry in children. A number of behavioral problems are presented to the child neurologist as a primary or secondary symptom in the normal or developmentally delayed child ***(Gosalakkal, 2003).***

Problems with distractibility and ADHD are frequently seen in CWE ***(Schubert, 2005).*** Deficits in sustained attention have been found more consistently than deficits in selective or divided attention ***(Sanchez-Carpintero & Neville, 2003).***

Inattentiveness may be a partial explanation for the increased prevalence of learning disorders in CWE and with normal intelligence. After controlling for intelligence, attention was found to be a better predictor of academic success in CWE than memory, self-esteem, or socioeconomic factors ***(Williams et al., 2001).***

Inattention and hyperactivity are two of the behavioral symptoms commonly reported in association with childhood epilepsy. As children with epilepsy are at known risk for academic underachievement, inattention and hyperactivity may be important as potential explanations for the school difficulties they experience. Therefore, appropriate treatment of attention problems might improve the scholastic abilities of these children ***(Dunn et al., 2003).***

The prevalence of ADHD in epilepsy populations has varied widely depending on the sample studied and the measures for ADHD used. Studies using epilepsy clinic populations have reported symptoms of ADHD in 8 to 77% of children. Old studies found that 8% of the children with epilepsy had inattention, overactivity, and distractibility plus aggression and mood lability. By current diagnostic practices, these children would merit a diagnosis of ADHD plus a comorbid conduct or mood disorder or, possibly, juvenile onset bipolar disorder. More recent studies conducted on children with epileptic encephalopathy, found that 77% had at least one symptom of ADHD reported by a parent or teacher ***(Dunn et al., 2003).***

The children with epilepsy had significantly more problems with attention than expected from general population normative values. This was also supported by the significant elevation of CBCL mean scores for attention in these children. It was also found that more children with generalized seizures had a symptoms of ADHD compared with children with partial or absence seizures ***(Dunn et al., 2003).***

ADHD seen in the child psychiatric clinic may be due to impairment in the prefrontal-striatal pathways. However, there are more widespread neural systems involved in attention. Epilepsy, including the underlying CNS lesion, the repetitive electrical discharges, and AEDs, may cause dysfunction in multiple areas of the CNS, thus causing inattention without the hyperactivity seen in traditional ADHD ***(Dunn et al., 2003).*** Problems with attention and ADHD appear to be specifically related to epilepsy and not just a response to a chronic illness. CWE had more problems with attention than children with other chronic disorders ***(Rodenburg et al., 2005b).***

Epilepsy may have a broader impact on multiple attentional networks within the central nervous system. Recent neuropsychological assessments in children with epilepsy have shown below-average verbal and visual attention skills, slowing of psychomotor speed, and

impairment in sequential cognitive processing ***(Haverkamp et al., 2001).***

There are several possible explanations for the association between epilepsy and symptoms of ADHD. Risk factors might include neurological dysfunction, seizure variable, medication effects, or psychosocial response to epilepsy. We think neurological dysfunction or seizure variables may contribute to the increased risk for symptoms of ADHD ***(Dunn et al., 2003).*** The risk factors most consistently associated with inattentiveness in CWE are intractable seizures, and certain AEDs, such as barbiturates and benzodiazepines, and to a lesser extent topiramate, zonisamide, and vigabatrin ***(Aldenkamp et al., 2003).*** Sex has not been a consistent predictor of ADHD in CWE. Neither seizure type nor localization of seizure focus (e.g., frontal, temporal, central spike focus with generalized discharges) has consistently predicted ADHD ***(Dunn et al., 2003).*** Seizure frequency may be an important risk factor because frequent non-convulsive seizures (i.e., absence seizures) were associated with attention deficits and slow information processing ***(Aldenkamp and Arends, 2004).***

Austin et al. (2001) found that children with new-onset seizures had significantly more attention problems as measured by the CBCL than siblings, suggesting an underlying neurological dysfunction caused both seizures and attention problems. In addition, when the sample of children with new-onset seizures were divided into those

with apparent first seizures and those with prior unrecognized seizures, 15.8% of the children with prior unrecognized seizures were in the clinical range for attention problems based on CBCL scores versus 8.1% of those with apparent new-onset seizures and 3% of siblings. This could be due to disruption of attention through transient cognitive impairment from subclinical epileptiform discharges. Barkley (1998) has noted that psychosocial factors are not a significant contributor to the etiology of ADHD but may be important in the severity and persistence of symptoms ***(Dunn et al., 2003).***

Recent studies have suggested that psychiatric pathology could be a risk factor for the development of unprovoked non-febrile seizures and epilepsy in children. For example, a retrospective cohort study was conducted on 133,440 pediatric patients (ages 6–17 years) without a history of seizures or prior use of anticonvulsant medications. The data source for this study was a research database containing pharmacy and medical claims for members of a large US-based managed healthcare organization. The incidence rate of seizures among children without psychiatric diagnoses was 149 per 1, 00,000 person-years, while that among children with psychiatric diagnoses, other than ADHD, was 513 per 1,00,000 person-years ***(Kanner, 2008).***

Epilepsy may be more common in children with ADHD compared with normal controls. In a population-based, case-control study of all newly diagnosed,

unprovoked seizures among Icelandic children, ages 3–16 years, it was found that a history of ADHD was 2.5-fold more common among children with newly diagnosed seizures than among control subjects. The investigators used the Diagnostic Interview Schedule for Children to make a DSM-IV diagnosis of ADHD in a standardized fashion among cases and controls, who were the next two same-sex births listed in the population registry. The association was restricted to ADHD of the predominantly inattentive type and was not seen with ADHD of the predominantly hyperactive–impulsive or combined types. Seizure type, etiology, sex, and seizure frequency at diagnosis (≥1) did not have any impact on the findings. These data suggest that epilepsy shares common pathogenic mechanisms with ADHD, mood, and anxiety disorders, which facilitates the occurrence of the seizure disorder in the presence of the psychiatric disorder and vice versa ***(Hesdorffer et al., 2004).***

A first recommendation is to enhance seizure control and remove AEDs when they demonstrate adverse effect on attention. Promoting sleep efficacy also may be helpful. Current practice parameters recommend stimulant medication for ADHD, but there are concerns about precipitating seizures or increasing seizure number. Although no large controlled studies are available, several open-label studies have suggested that stimulants are probably both safe and effective for CWE and ADHD ***(Plioplys et al., 2007).***

Although other non-stimulant medications such as bupropion and the tricyclic antidepressants can be effective in the treatment of ADHD, they should not be used in CWE because both bupropion and the tricyclics may lower seizure threshold. Although the data are limited, it seems safe to conclude that stimulants are safe and effective in children with well controlled seizures, in children with ADHD and abnormal EEGs and are probably safe and effective in those with active epilepsy. Atomoxetine may be a good alternative, although additional information is needed ***(Plioplys et al., 2007).***

Other disruptive disorders, such as oppositional defiant disorder and conduct disorder, are not more prevalent in this clinical group when compared to the general population ***(Plioplys, 2003a).*** Yet, Dunn (2001), found an increased risk in young people with epilepsy of developing ODD or CD, which ranged from 10 to 35% ***(Dunn and Austin, 2004).***

***Aggression:***

One of the more common behavioral problems seen in children is aggression and dyscontrol ***(Gosalakkal, 2003).*** Aggression in children and adolescents with epilepsy has proved harder to define ***(Dunn and Austin, 2004).*** There is a paucity of research exploring intermittent spontaneous aggression in children with epilepsy and mechanisms

underlying aggression in these children are poorly understood ***(Elliot et al., 2004).***

Physical and verbal aggression may also be a symptom of frontal lobe epilepsy in children in association with other psychological deficits. Rage outbursts and increased aggression have been noted to occur in higher rates in children with temporal lobe epilepsy. Some researchers argued that the dyscontrol syndrome was a product of limbic dysfunction and that many patients improved on anticonvulsants. Some children with complex partial seizures do exhibit episodic dyscontrol interictally. There is an increased incidence of rage attacks in children with attention deficit disorder and temporal and frontal lobe injury ***(Gosalakkal, 2003).***

Ictal acts of aggression are rare in children. It is unprovoked and usually not directed towards an individual and cannot usually be modified during the event. Resistive violence is more common than ictal aggression. This happens when attempts are made the patient reacts with aggression ***(Gosalakkal, 2003).*** Aggressive behavior can occur particularly in association with postictal confusion and during those rare cases of postictal psychosis ***(Dunn and Austin, 2004).*** It is difficult to always attribute interictal aggression to the epilepsy itself. Both epilepsy and abnormal behavior may be related to brain malfunction. Children with epilepsy may be subjected to ridicule and rejection leading to

low self-esteem and potential behavioral abnormalities ***(Gosalakkal, 2003).***

Many parents in clinical setting describe a variety of scenarios in which they have observed changes in their child's mood accompanied by increased aggression. The most frequently cited complaint is that introduction or high doses of certain antiepileptic medications coincide with behavioral changes including irritability, verbal, or even physical aggression. For example, this might take the form of a younger child hitting other children. If the behavioral side effects are intolerable, reducing or discontinuing the antiepileptic medication while adding another medication may be necessary. Second, behavioral changes, such as increased irritability and verbal or physical aggression, often herald the onset of a seizure. These behavioral changes can occur minutes to days before a seizure. During this period, certain triggers (stimuli) may further irritate the child, producing increased frustration or aggression. Therefore, it may be prudent to reduce over stimulation in the school setting during this period, for example decreasing academic workload. The third scenario comprises a smaller group of children who experience sudden outbursts of verbal or physical aggression. These children present special challenges to the family, school and health professionals ***(Elliot et al., 2004).***

Characteristically, the episode of aggressive behavior may appear with minimal or no provocation and can go on

for some time. Clinical observations, as well as conversations with children, parents, and teachers suggest a trajectory for episodic verbal or physical aggression. It seems that the child perceives a certain situation as noxious. For example, some children with epilepsy may have very sensitive hearing. Loud noises or a confusing number of noises in the classroom might precipitate explosive behavior. Once the trigger stimulates an angry feeling, it is difficult for these children to 'put on the brakes'. It is not that they 'won't' control their aggression; rather, children tell us that they 'cannot' control the aggressive outbursts. Parents report that children often experience remorse following an aggressive outburst. They frequently berate themselves, for example, saying, "I'm a bad person". Interventions that focus on immediately removing the stimulus/trigger, or removing the child from the stimulus, can sometimes diffuse their anger and outburst. It was reported that these children did not respond to standard behavioral management strategies or restraint alone. Rather a combination of strategies, including assessment and follow-up by psychiatry, and interventions such as psychotropic medications and/or intensive behavioral therapy, may be warranted ***(Elliot et al., 2004).***

***<u>Mood & Anxiety disorders:</u>***

The epilepsies are a complex group of disorders commonly associated with brain dysfunction in the form of behavioral and cognitive affection in children, in addition to social isolation, and vocational difficulty ***(Hecimovic et al.,***

***2003).*** The unpredictable nature and course of epilepsy may have a significant impact on both the physical and psychosocial functioning of the child and the family ***(Baki et al., 2004).*** Each of these factors may contribute to increased prevalence of depressive disorders in epilepsy, but the specific mechanisms are not completely understood ***(Hecimovic et al., 2003).***

Depression in persons with epilepsy may be related to biologic factors (e.g., familial predispositions to mood disorders, the effect of seizures on mood regulation, and the effects of antiepileptic drugs), as well as to psychosocial factors (e.g., fear of experiencing seizure recurrences, stigmatization) ***(Strine et al., 2005).***

Depression is a common but often overlooked problem in epilepsy. In part, this may be the result of differences in symptoms of depression in children versus those seen in adults. Children more often present with irritability, withdrawal, somatic complaints, and trouble sleeping. Difficulties with concentration may lead to school failure. Adolescents may have similar complaints but also develop hopelessness, guilt, and suicidal ideation. A family history of mood disorder may be an important clue to the diagnosis of depression in children with epilepsy ***(Plioplys, 2003b).***

Depression is the most frequent psychiatric co-morbidity in patients with epilepsy. By the same token patients with depression are at higher risk of developing

epilepsy than are controls. In population based, case control study carried out in patients with newly diagnosed epilepsy, some researchers found that a history of depression (preceding the onset of epilepsy) was seven times more frequent among patients than among age and sex matched controls ***(Kanner, 2005).***

Children and adolescents with epilepsy also are at increased risk for depression, as documented in a number of previous studies. In the general population, the prevalence rates of depression in children and adolescents range from 2 to 9% ***(Baki et al., 2004).*** The rate of depression in children and adolescents with epilepsy is 12-26% of these patients, which is much higher than that observed in general population. This wide range reflects methodologic differences, such as differences in types of diagnostic instruments (e.g., structured psychiatric interviews, self-report scales), number and type of informants (e.g., child, parent, teacher), diagnostic end points (e.g., Diagnostic and Statistical Manual of Mental Disorders-IV {DSM-IV}, clinical diagnosis), age range of subjects (e.g., children, adolescents), recruitment sources (e.g., community samples, university-affiliated clinics), chronicity of study samples (new-onset seizures, chronic epilepsy, postsurgical patients), and sample size ***(Caplan et al., 2005).***

Data of many studies suggest a bidirectional relation between depression and epilepsy; they cannot be interpreted

as an indication of a causal relation. However, the high co-morbidity prevalence rates of these two disorders suggest that depression and epilepsy may share pathogenic mechanisms. Abnormalities of serotonergic and noradrenergic transmission are pivotal pathogenic mechanisms of mood disorders. Decreased serotonergic and noradrenergic activity facilitates the kindling process of seizure foci, exacerbates seizure severity, and intensifies seizure predisposition in some animal models of epilepsy ***(Kanner, 2005).***

A review of literature reveals structural and functional abnormalities of the same neuroanatomic regions in primary depression and in epileptic seizure disorders. In epilepsy, relevant areas include mesial and orbitofrontal regions as well as mesial temopal and cubcortical structures, such as thalamic nuclei. In primary depression, researchers described the existence of morphologic and volumetric changes in various neuroanatomic structures that form a 'limbic-cortical-striatal-pallidal-thalamic tract'. The tract consists of two branches: (1) a limbic-thalamic-cortical branch that include amygdala, hippocampus, and medial-dorsal nucleus of the thalamus as well as the mesial and ventrolateral prefrontal cortex; and (2) a branch running in parallel and linking the caudate, putamen, and globus pallidus with limbic and cortical regions. It is not surprising to find prevalence rates of depression ranging from 19%-65% among patients with epilepsy of mesial temporal or frontal lobe origin ***(Kanner, 2005).***

Neuroimaging studies in epilepsy also support the association of dysfunction in specific brain regions with the presence of symptoms of depression, that there was significant association of mesial temporal sclerosis with increased Beck Depression Inventory (BDI) scores, and other investigators report an association of depressive symptoms with abnormalities of blood flow and glucose metabolism in frontal or temporal brain regions ***(Hecimovic et al., 2003).***

An understanding of childhood depression requires evaluation of the relationships between biological, social, and iatrogenic risk factors and negative life events ***(Baki et al., 2004).*** Depression in children with epilepsy is associated with family discord, number of stressful life events, broken homes, and family history of depression. Psychosocial variables that might contribute to learned helplessness, such as decreased satisfaction with family relationships, negative attitude toward illness, and unknown or external locus of control were associated with higher CDI scores in adolescents with depression. Although social difficulties can trigger depression in the general child and adolescent population, their role has not been studied in mood disorders co-morbid with pediatric epilepsy ***(Caplan et al., 2005).*** Most of the biological explanations for depression in the population with epilepsy have focused on seizure type and lateralization of epileptic foci. In the majority of studies, electroencephalographic findings and age of onset have not

been associated with depression in children, but seizure recurrence, high frequency, and longer duration of epilepsy have been found to be associated with depression ***(Baki et al., 2004).***

Regarding predictors of mood disorder in children and adolescents, as found in the general population, a gender effect is found, with more depression in adolescent girls with epilepsy, and an age effect with higher depression rates in adolescents compared with children with epilepsy. Some studies report no association with seizure variables, and others report an association with seizure frequency, antiepileptic drug polytherapy, type of antiepileptic drug, and duration of illness ***(Caplan et al., 2005).***

Prevalence rates for anxiety disorders in adults with epilepsy range from 14 to 78%. However, few studies have examined anxiety in children with epilepsy and the prevalence remains unknown. In adult patients with epilepsy, many risk factors predisposing to the development of anxiety, including neurological, pharmacological, and psychosocial factors, have been identified. Among the neurological factors, severity of epilepsy has been associated with increased anxiety; however, other disease-related factors have not been shown to be predictive of anxiety in children with epilepsy. Among the psychosocial factors, unpredictability of seizures, fear of death, parental reactions of distress and fear, restrictions on normal living and activities, stigmatization and social rejection, misinformation

about the disorder, and the resulting low self-esteem may predispose children and adolescents to anxiety and negative affective responses. Antiepileptic drugs (AEDs) can also contribute to the development of anxiety or depression, either as a side effect or because of withdrawal ***(Baki et al., 2004).*** Anxiety is also more common in children who have intractable seizures and in those who are on multiple AEDs ***(Ettinger et al., 1998).***

Parental anxiety, which may result in restriction of activities, has been reported to be associated with decreased quality of life for both the child and family. These findings suggest that parental anxiety may have an impact on parenting behaviors. Highly anxious parents may be more likely to perceive higher risks for their children and misinterpret information about their child's condition. Transmission of parental anxiety to the child concerning health status is hypothesized to be a psychological risk for the child. Whether behavioral changes associated with parental anxiety interfere with the process of parent–child separation and independence is unknown ***(Baki et al., 2004).***

Given the internalizing nature of the symptoms of affective and anxiety disorders, informants, such as parents, are frequently unaware of mood and anxiety symptoms their children experience. In addition, parents' psychiatric status might influence what and how they communicate information. Thus depressed and anxious parents might be aware of their children's symptoms, but underestimate or

downplay the severity of these symptoms. Parents might also unwittingly perceive epilepsy-related phenomena as abnormal behaviors ***(Caplan et al., 2005).***

Ettinger et al. study was the first one to examine and demonstrate significantly increased rates of self reported symptoms of anxiety and depression among pediatric patients with epilepsy. That no patient in their study was previously diagnosed with a mood disorder, and the paucity of other previously published information in this regard, suggest that such symptoms may be poorly recognized in pediatric patients with epilepsy ***(Ettinger et al., 1998).***

Although adults may express depression or anxiety more directly, pediatric patients may present with other signs, such as disruptive behaviors or irritability, which may not be readily identified as signs of depression or anxiety. Alternatively, they may present no obvious behavioral signs. A study suggests that if health care providers do not inquire directly about potential depressive or anxiety-related symptomatology, such symptoms may not be detected ***(Ettinger et al., 1998).***

Although increases in mean CDI scores have been reported in several other pediatric disorders such as migraine or diabetes mellitus, several factors may contribute to emotional symptoms in the specific disorder of epilepsy. These influences include CNS variables (e.g., effects of seizures, concomitant CNS conditions giving rise to seizures,

and medications), as well as psychosocial factors (e.g., the stigma of having seizures). In one study, external locus of control (which tends to correlate with depression and anxiety) was higher among children with epilepsy as compared with matched normal and diabetic controls ***(Ettinger et al., 1998).***

Some studies found that epileptic children have significantly higher levels of trait anxiety than normal controls. The number of studies that have examined anxiety in children with epilepsy is small, and the prevalence remains unknown. Most studies suggest an association between the presence of epilepsy and anxiety in children. Gender, age, age of seizure onset, and seizure type were not associated with anxiety in some studies. In contrast, in other studies, higher seizure frequency was associated with increased anxiety in young or old children, and longer duration of epilepsy was associated with increased anxiety only in the older group. Some studies have suggested that higher seizure frequency or epilepsy duration is associated with increased anxiety ***(Baki et al., 2004).***

The finding of an association between long duration of epilepsy and the presence of co-morbid anxiety is of interest. Both neurobiological and psychosocial processes may explain and contribute to this association. From the biological viewpoint, the limbic structures could potentially play a role in the genesis of both disorders (epilepsy and anxiety). On

the other hand, a long history of refractory epilepsy would confer significant uncertainty, fear of seizures, restrictions in lifestyle, and considerable social disadvantage on these individuals. Such a climate of psychological adversity is commonly associated with the development of anxiety, thus explaining this association ***(Satishchandra et al., 2003).***

As a conclusion, studies vary in their findings regarding variables associated with depression and anxiety in youth with epilepsy. Some find an association with seizure variables, such as seizure control, AED polytherapy, age of onset, duration of illness, and type of epilepsy, but others do not. Subtle cognitive deficits, low IQ, co-morbid learning difficulties, neurological disabilities, and sex and age are predictors of depression in children with epilepsy ***(Plioplys et al., 2007).***

***Suicidality:***

Previous studies reported high representation of epilepsy disorders among suicidal pediatric patients, which suggest that clinicians must be alert to symptoms of depression and anxiety and even suicidal ideation ***(Ettinger et al., 1998).*** Caplan et al. (2004) examined suicidal behavior in a large sample of children with epilepsy and the association with psychopathology, cognition, language and seizure variables ***(Martin, 2004).***

Only a few studies, however, examined suicidality in children with epilepsy. Ott et al. (2001) reported suicidal ideation in 17% of 48 CPS and 18% of 39 CAE and suicidal intent in 8% and 11% of CPS and CAE groups, respectively, but these rates were not significantly higher than those in 59 normal children (9% ideation, 1% intent). Ettinger et al. (1998) identified suicidal ideation with intent in 4.3% and without intent in 11% of children with epilepsy. Among 15 children with epilepsy treated with phenobarbital, it was found suicidal ideation in 40% compared only 4% of 24 children with epilepsy treated with carbamazepine. Other than the reported association with phenobarbital, no similar studies have evaluated the relation between suicidal ideation and seizure variables in children with epilepsy ***(Caplan et al., 2005).***

Most patients with affective and anxiety disorders had anxiety more than depression, whereas the most frequent diagnosis among those with suicidal ideation was co-morbid affective/anxiety and disruptive disorders. The presence of affective and anxiety disorders was related to age and verbal IQ deficits in addition to school difficulties, and the presence of suicidal ideation, to increased duration of illness. Scholastic achievement might make children with epilepsy vulnerable to mood disorders by affecting self-esteem and cognitive flexibility, variables related to mood disorders in children. Depression was more frequent in the CPS patients, and anxiety disorders in the CAE patients ***(Caplan et al., 2005).***

What Caplan et al. (2004) found was that children with complex partial seizures or childhood absence epilepsy with average intelligence had significantly higher rates of psychiatric disorders than children in the general population and than what has been described among children with chronic illness. Furthermore, although none of the children with epilepsy in the study had made a suicide attempt, the children with epilepsy had a significantly higher rate of suicidal ideation/plan (20%) than the healthy group (9%). Among the 34 patients with suicidal ideation/plan, 79% had a DSM-IV diagnosis compared to 52% in those without suicidal ideation/plan ***(Martin, 2004).***

It was found that depression was not the psychiatric diagnosis most commonly associated with suicidal behavior. In addition, the increased frequency of co-morbid disruptive and affective/anxiety disorders imply that impulsivity, which plays a role in adolescent suicide, particularly in boys, might be implicated in the suicidal ideation of children with epilepsy ***(Caplan et al., 2005).***

Clinicians tend to focus more on seizure control when treating children with epilepsy and do not acknowledge as much as we should the underlying psychological ramifications and the impact of epilepsy on behavior of kids. Currently, psychiatric evaluations are not commonplace diagnostic tools used by pediatric neurologists. Caplan speculates that part of the reason for the lack of psychiatric

evaluations in children with epilepsy is due in part to a lack of knowledge within the scientific community regarding suicidal ideation in the pediatric population ***(Martin, 2004).***

Of note, studies using structured psychiatric interviews have not described bipolar disorder diagnoses in CWE. It is unclear whether this reflects a low base rate of this disorder in pediatric epilepsy, the mood stabilizing effect of AEDs, the type of diagnostic instruments, or the diagnostic practices of child psychiatrists who work with CWE. Studies of children with epilepsy imply that bipolar disorder may be rare in pediatric epilepsy ***(Rodenburg et al., 2005a).*** Studies are clearly needed to ascertain the incidence of bipolar disorder and how this is related to AED treatment of CWE ***(Plioplys et al., 2007).***

As regards the management of co-morbid depression with epilepsy, few studies were done. Among which it was found that selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacological treatment agents for depression and anxiety in CWE. Drug interactions between SSRIs and AEDs occur because they use the same CYP450 and 2D6 metabolic system in the liver. Elevation of serum phenytoin and valproic acid levels has been reported after introduction of SSRIs ***(Plioplys et al., 2007).*** Other antidepressants may be considered if SSRIs fail. Although trazodone and nefazodone can be effective, they are often associated with lethargy. Venlafaxine and bupropion have

been associated with a moderately increased risk of seizures ***(Dunn and Austin, 2004).***

# ***Neuropsychological deficits in children with epilepsy & the effect of AEDs***

There are many reasons why epilepsy may be associated with learning and behavioral difficulties. Casual relationships are complex. Earlier studies reported that seizure type, frequency, duration, and age of onset was associated with greater or lesser degrees of neuro-psychological impairment. Seizure frequency is important variable affecting cognition. Intellectual dysfunction was common in children with intractable seizures ***(Cormack et al., 2007).***

Many children with epilepsy have impaired cognition, memory and learning, whereas other children with seizures have no neurocognitive deficits. Even if seizures are well controlled, children and adolescents with epilepsy may function less well than expected in school, family and community activities ***(Leonard & George, 1999).*** In clinical studies higher seizure frequency significantly correlated with lower IQ scores, poor attention, and language skills ***(Nolan et al., 2003).***

The more frequent the seizures the greater the likelihood that cognition will be impaired. Within each seizure type, lower seizure frequency was associated with higher IQ. Patients with a shorter duration of seizures

performed slightly better across various cognitive measures ***(Leonard & George, 1999).***

Seizure type is another variable that affects cognitive performance of children with epilepsy. Children with generalized convulsive seizures have slightly poorer mental abilities than with other seizure types. Myoclonic, tonic, atonic, clonic and generalized seizures are associated with the poorest ability. Absence and partial seizures are not often associated with substantial losses in abilities unless there are other associated factors ***(Dodrill, 1992).***

Age of onset is an important variable that affects children's cognition. Early onset of epilepsy is associated with increased risk of cognitive impairment ***(Smith et al., 2002).*** Data from children with a variety of epilepsy syndromes suggest that epilepsy occurring in early childhood is frequently associated with considerable cognitive and behavioral morbidity ***(Vasconcellos et al., 2001).*** Some researchers found the most cognitive impairment in children with seizure onset in the first year of life. Depending on the relative vulnerability of various parts of the brain and individual susceptibility, the consequences of epileptiform discharges may be different even if the age of onset, seizure type, severity and duration all appear to be the same. Cognitive disturbances in epileptic children vary depending on the age of onset, seizure type, EEG pattern and selection of anticonvulsants ***(Leonard & George, 1999).***

Epileptic discharges can start during infancy in brain areas that are important for later developing higher cortical functions. Learning, practice and experience are critical for mastery and consolidation of complex neurocognitive functions. Cortical and subcortical pathways on which higher cognitive functions depend may be impaired because of a functional epileptic disconnection and result in failure to acquire or aberrant development of selected cognitive skills ***(Leonard & George, 1999).***

Although overall intellectual ability in children with epilepsy is comparable to the normal childhood population they are at greater risk for learning problems and academic under achievement. Even in those with normal intelligence, reports of deficits in specific areas related to thinking and learning abilities are common, particularly in the areas of attention and concentration, memory, organizational skills and academic achievement ***(Elliot et al., 2004).*** Motor speed and perceptual-motor functions are widely reported. Deficits in problem solving abilities, neurolinguistic processing, visual-spatial function and discrete learning abilities affecting word recognition, reading comprehension, spelling and arithmetic have also been reported ***(Leonard & George, 1999).*** Indeed, many children do not fit the typical school definition of learning disabilities, as their reading, spelling and math skills may be appropriately developed ***(Elliot et al., 2004).***

Deficits in sustained attention are often reported in children with epilepsy. Epileptic patients with normal intelligence differed from normal peers in reaction time and attention, but not impulsivity. Differences in motor speed were greater for non-dominant hand speed than for the dominant hand. Cognitively impaired epileptic patients had more impairment on reaction time measures. Higher medication doses affect reaction time and vigilance. Children on monotherapy tended to perform better than patients requiring polypharmacy ***(Leonard & George, 1999).*** Children who have a scar in the middle part of the temporal lobe (mesial temporal sclerosis) may have permanent short term auditory or visual memory problems ***(Elliot et al., 2004).***

Three specific types of learning dysfunction were postulated in children with epilepsy. First is a "memory-deficit type" with specific impairment in short term memory and memory span. A "speed-factor" is the second type, with slowing of information processing skills especially on complex tasks. Third, impaired "problem solving" is involved in higher order cognitive function processing tasks such as concept formation, logical thinking, decision making and verbal reasoning ***(Aldenkamp et al., 1990).***

Temporary disturbances in mental functioning may occur during or immediately after epileptic discharges ***(Leonard & George, 1999).*** For example, seizures and post-seizure fatigue or confusion (post ictal state) can disrupt learning for minutes or hours ***(Elliot et al., 2004).*** There are

the brief lapses of consciousness in childhood absences that disrupt information processing. Isolated cognitive or behavioral deficits may result from epileptic discharges starting in focal cortical areas responsible for higher order functions, such as language regions producing transient dysphasia. Measures of choice reaction time, sustained attention and immediate memory can also be affected during epileptic discharges ***(Leonard & George, 1999).*** Although it is well known that visible seizures interrupt learning, there is some evidence that epileptiform discharges which occur in the brain between seizures (interictal activity) may also disrupt learning. This is referred to as Transient Cognitive Impairment (TCI) ***(Elliot et al., 2004).***

Children with poorly controlled epilepsy, children themselves frequently cited fatigue as an important factor that decreased their availability to learn in school. It is likely that these transitory disruptions in learning account for parent and teacher reports that academic performance in these often children fluctuates from day-to-day. Teaching and learning strategies that take into account the dynamic learning profile of these children, for example intensive programs that utilize repetitive instruction techniques, are critical to the child's academic success ***(Elliot et al., 2004).***

With regard to hemispheric specialization, left sided epileptiform discharges affect predominantly verbal tasks, while right sided discharges affect non-verbal skills in most individuals. A temporary regression in behavior, language or

any other specific cognitive ability can be a symptom of focal epilepsy originating in cerebral areas involved with frontal or temporal regions. Modality specific or general decline in cognitive functions can result from prolonged or repeated postictal deficits and may occur over hours, days, or even weeks ***(Leonard & George, 1999).***

Symptomatic epilepsy, however, appears to be associated with cognitive delay and behavioral problems. In population-based longitudinal study, delay in adaptive functioning (communication, socialization, motor, and daily living) was found in children younger than 3 years of age with remote symptomatic epilepsy at the time of the initial diagnosis. Moreover, the delayed adaptive functioning of these children continues to decline over time and may lead to further loss or failure to develop new skills in the future ***(Berg et al., 2004).***

Schoenfeld et al. (1999) examined neuropsychological and behavioral status in a group of children with epilepsy who have complex partial seizures. These children are compared with a proper control group. The children underwent a comprehensive neuropsychological assessment which covers wide range of cognitive domains. For behavioral data the authors have depended on the Achenbach checklist (CBCL). The outcome is very clear-cut and draws attention to four significant findings:

- Firstly, there are significant cognitive impairments in the children even when social and familial factors are controlled for.

- Secondly, the authors noted that the profile of cognitive dysfunctions has specific features, namely both expressive and receptive language are particularly impaired. This profile is specific to this group of children with epilepsy. The pattern in other epilepsy may be different.

- Thirdly, the authors found impaired function in behavioral and social adjustment. The children do not have aggressive and delinquent behaviors, but the patterns include social withdrawal, somatic complaints, anxiety, and depression. Again, a different pattern might be observed in a different epileptic subgroup.

- The final findings highlight the predictors of neuropsychological status and behavioral adjustment. A finding of interests is that the frequency of seizures within the last year partly predicts the behavioral and social problems, but not the cognitive problems which are more associated with an early onset of the disease. It is tempting to hypothesize that the latter findings represent a more severe pattern of disease.

Therefore, caution should be taken in directly relating the frequency of the seizure to the behavioral phenomena and perhaps a loop exists to account for these findings. Naturally, there are other issues which would be liked to be

analyzed, most importantly the role of drugs and their undesirable side effects, which may affect both cognitive and behavioral issues ***(Bax, 1999).***

***<u>Cognitive & behavioral effects of AEDs:</u>***

During the past decade, only a few controlled trials have systematically examined the behavioral and cognitive side effects of AEDs in CWE ***(Aldenkamp & Alpherts, 2006).*** Although AEDs may produce cognitive side effects in vulnerable patients, it is unclear to what degree these cognitive side effects are associated with psychopathology ***(Aldenkamp et al., 2003).*** Therefore, available data regarding the specific casual effects of AEDs on the cognitive and behavioral problems in intellectually normal CWE are either insufficient or inconclusive ***(Plioplys et al., 2007).***

The American Academy of Pediatrics (AAP) Committee on Drugs (1995) concluded, "Few studies have been comprehensive, and for most drugs, neuropsychological effects have been incompletely described." Thus, major organizations representing both pediatrics and neurology emphasized the need to establish the neuropsychological profiles of newer AEDs in children and to determine the behavioral and cognitive consequences of long-term AED treatment on academic achievement and neuropsychological function to maximize treatment effectiveness ***(Loring, 2005).***

The use of AEDs in the management of epilepsy requires an ongoing risk benefit analysis that attempts to maximize seizure control while minimizing adverse cognitive side effects. AEDs can affect higher cognitive functions, motor function or both ***(Leonard & George, 1999).*** Certain psychiatric symptoms, such as behavioral activation (irritability, hyperactivity), disinhibition, and sleep problems, are known to be adverse reactions to specific AEDs, but this does not explain the development of comorbid psychiatric conditions in general ***(Plioplys, 2003a).***

Antiepileptic drugs decrease membrane excitability, increase postsynaptic inhibition or alter synchronization of neural networks to decrease excessive neuronal excitability associated with seizure development. Common side effects of decreasing neuronal excitability, however, are slowed motor and psychomotor speed, poorer attention and mild memory impairment ***(Loring, 2005).*** Studies in rats have shown significant AED effects in the developing brain including apoptotic neurodegeneration ***(Olney et al., 2002).*** Initial studies with children suggest that the effects of major AEDs are comparable across developmental life span. However, during the formative years of a child's intellectual development, close scrutiny should be paid to subtle attentional factors that could contribute to cumulative deficits in learning or memory ***(Leonard & George, 1999).***

Phenobarbital and traditional benzodiazepines are associated with the greatest risk of cognitive side effects. In studies, children on phenobarbital displayed IQ declines, and although IQ improved following discontinuation of phenobarbital there continued to be long-term achievement effects when these children were tested three to five years later ***(Sulzbacher et al., 1999).*** The inability of children to fully catch up and compensate for "lost time" is important because it suggests a more complex interaction of AED therapy and developmental maturation than simply interfering with new learning efficiency ***(Loring, 2005).*** Phenobarbital has been associated with depression and an increased risk of suicide ***(Dunn & Austin, 2004)***, and sometimes aggression ***(Bourgeois, 1998).***

Thus, long-term AED side effects should be considered when selecting an AED for pediatric use. AEDs can affect higher cognitive functions, motor function or both. The cognitive effects of major AEDs including phenytoin, carbamazepine, and valproate, appear modest when dosages are kept within standard therapeutic ranges and polypharmacy is avoided. Polypharmacy or dosages that exceed the standard therapeutic range, increases the risk of alterations in arousal, attention, memory and psychomotor functioning ***(Loring, 2005).***

Neuropsychological side effects generally emerge according to a dose-dependent relationship; however, both quality of life and memory may be affected, even when

serum blood concentrations are within standard therapeutic ranges. In addition, some children are at heightened risk for developing disproportionate cognitive side effects with carbamazepine ***(Loring, 2005).***

There are virtually no formal neuropsychological investigations of the recently introduced AEDs in children ***(Loring, 2005).*** Initial studies involving, the newer AEDs suggest that the cognitive profile of these drugs is favorable, but further research is needed to determine their relative effect on each other and to older AEDs ***(Leonard & George, 1999).*** Newer AEDs whose mechanism is GABAergic, such as levetiracetam, topiramate, tiagabine, and zonisamide, have caused depressive symptoms ***(Dunn & Austin, 2004).*** Anxiety or nervousness has been seen with activating drugs such as felbamate and topiramate and with withdrawal of AEDs ***(Vazquez & Devinsky, 2003).*** Aggression has been associated with felbamate, vigabatrin, and gabapentin ***(Bourgeois, 1998).***

# ***Quality of life in children with epilepsy Psychosocial aspects & Impact on family functioning***

Through history, epilepsy had been considered a stigmatized condition. Unfortunately this remains true today despite progress in medical science, as the diagnosis of epilepsy can still have a profound social and psychological impact on patients and their families because of others' lack of information ***(Fernandes et al., 2005).***

In the recent years, apart from the effective therapeutic management of epilepsy, the cognitive and psychiatric impact of the illness and various medications used to treat it are to be taken primary care of. This role requires a strong primary psychiatric background that enables the psychiatrist to understand the psychosocial impact that epilepsy, a chronic illness, can have and how epilepsy related cognitive deficits may affect patient's educational and employment opportunities and hence their sense of control and independence ***(Raguraman & Wadoo, 2006).***

The general understanding of epilepsy has been enhanced by the efforts of concerned people. However, prejudice and misunderstanding still exist, and the current situation is still unsatisfactory. Techniques for diagnosis and treatment of epilepsy have significantly advanced, but

improving the quality of life for children with epilepsy remains an important problem ***(Hanai, 1996).***

The lack of information has been indicated as an important factor in stigma perpetuation. Interestingly, surveys in developing countries with different cultures reveal common beliefs, for example, that epilepsy is a contagious illness or a kind of mental retardation. In addition, some people do not know what to do with a person during an epileptic seizure, which promotes a feeling of impotence and reinforces the misconception that epilepsy has no treatment. The spontaneous thoughts may reflect society's collective unconsciousness of prejudice toward epilepsy and people with epilepsy ***(Fernandes et al., 2005).***

A study conducted on 29 children, to survey children's perception of epilepsy, revealed that 24% of the children perceived epilepsy as "disease that can kill", 20% as "I don't know", 16% as "disease of swallowing the tongue", 16% as "contagious disease", 12% as "only a disease", 8% as serious illness, and 4% as "head injury" ***(Fernandes et al., 2005).***

In developing countries, negative attitudes and stigma appear to be more prevalent compared to the western world. Parental adjustment is a particularly important target because of these negative attitudes toward disability in general and epilepsy in particular. For example, in surveys from India and Taiwan 15% and 7% of respondents, respectively, believed epilepsy to be a form of insanity; 40%

and 18%, respectively, believed that CWE should not go to school or that their children should not play with them; and 66% and 72%, respectively, objected to their children marrying someone who had ever had epilepsy. In Taiwan, 31% believed that people with epilepsy should not be employed in jobs as other persons are (***Ronen et al., 2003).*** Research on lay attitudes towards people with epilepsy has revealed that they are perceived as sexually deviant, antisocial, aggressive, potentially violent, mentally ill and unattractive (***Spangenberg & Lalkhen, 2006).***

Correct knowledge of epilepsy and education is very important. It is necessary to propagate accurate knowledge regarding epilepsy to all professional groups that relate to children with epilepsy, as well as to the general public, in an effort to abolish prejudice and misunderstanding about epilepsy ***(Hanai, 1996).*** Knowledge about epilepsy and its implications and taking shared responsibility for treatment promote a sense of control and competency among family members (***Spangenberg & Lalkhen, 2006).***

Epilepsy is characterized by its episodic and chronic nature. The seizures usually produce brief periods of disruption, which include phenomena such as loss of consciousness, bodily distortion, injuries, unusual and often frightening psychological experiences as well as urinary and bowel incontinence ***(Ronen et al., 2003).*** Children with epilepsy are often overwhelmed by feelings of embarrassment, frustration and helplessness and display

resultant fearfulness, dependence and demanding behavior ***(Spangenberg & Lalkhen, 2006).*** Apart from the episodic seizures, there are many other ever-present factors – social, psychological, behavioral, educational, cultural and so forth – which affect the lives of children with epilepsy (CWE), their families and their close social networks. These factors vary considerably from one person to the next, but have a significant impact on the daily quality of life in every affected individual ***(Ronen et al., 2003).***

It was concluded that although the effort to control seizures is of primary importance, there remain many problems concerning the psychological management of the child and his or her parents and their relationship to the social milieu in which they live. There is ample scientific evidence to confirm this opinion regarding poor psychosocial outcome in childhood onset epilepsy ***(Ronen et al., 2003).***

Most people with disabilities or chronic illness strive to gain the same quality of life or functional well-being as healthy individuals. Children with epilepsy and their families are no different ***(Ronen et al., 1999).*** Families of children with more frequent seizures experience greater psychological stress. Parents may feel angry at each other and at times at their child. Parents experience fear about epilepsy and its consequences, including the potential for self injury from falls, mental abnormality, and behavioral problems. Family reactions may range from overprotection to

scapegoating and rejection. Various behaviors are associated with parental reactions, including ostracism, overindulgence, alterations in family activities, sibling jealousy and decreased parental expectations of the epileptic child. Recurring seizures interfere with the child's ability to adjust to age appropriate tasks. Children with epilepsy may experience guilt, concealment, adoption of a sick role with deterioration in age appropriate skills, withdrawal, denial, dependency and low self esteem ***(Leonard & George, 1999).***

In general pediatric population parental psychopathology, inadequate parenting, and an unstable family environment increase the risk for psychopathology ***(Pilowsky et al., 2006).*** Similarly, the quality of the parent-child relationship and parenting style has the strongest influence on psychopathology in CWE when other family factors, seizure-related variables, and child characteristics were controlled. Family risk factors specifically related to psychopathology in CWE include family mastery (i.e., the ability to organize the family environment), family adaptation to illness, overcontrolling parenting style, parent-child relationship, and maternal depression ***(Rodenburg et al., 2005a).***

The emotional impact of epilepsy on family members is a neglected topic, with the majority of studies confined to patients with epilepsy. Frequent seizures and accompanying injuries may lead to considerable emotional strain for family members, especially parents. Furthermore, parental beliefs

and attitudes concerning epilepsy may significantly impact adjustment for both the child and family. A negative social attitude toward disability has been reported to affect the adjustment of parents of children and adolescents with epilepsy, and parental adjustment has been reported to be inversely associated with the severity of the child's epilepsy. The relationship between parental anxiety and quality of life of children with epilepsy is not clearly understood ***(Baki et al., 2004).***

Families of children with frequent seizures suffer significantly more stress than families of children with infrequent seizures or of healthy controls ***(Ronan et al., 2003).*** Parents, particularly mothers, are frequently faced with the physical and emotional burden of dealing with the epileptic child ***(Jan, 2006).*** Mothers of children with additional psychiatric problems are found to have higher rates of psychiatric disturbances themselves ***(Ronan et al., 2003).*** Maternal fatigue may affect their productivity, social interactions, and their ability to adequately take care of their children ***(Jan, 2006).***

Sixty four Suadi-Arabian mothers of children with intractable epilepsy were examined for fatigue. Fatigue was measured using a standardized 11-item questionnaire. The study found that 44% of mothers suffered from fatigue. Several correlating factors were identified, mostly related to seizure control, mental and physical handicap ***(Jan, 2006).***

In terms of parental psychopathology, the severity of maternal depression has a significant relationship to psychopathology in CWE. Furthermore, mothers of CWE have higher rates of depression compared with mothers from a normative sample ***(Shore et al., 2004).*** Behavioral problems in children with epilepsy were found to be significantly associated with the presence of stress, psychiatric disorders in mothers, and intrusive parenting styles ***(Plioplys, 2003a).***

Parents' perceptions of their children are often based on images of the ideal child formulated during pregnancy. That image of an ideal child may be lost when a child is diagnosed with epilepsy. In part, this loss may result from the continued stigma associated with this diagnosis ***(Pal, 2003).*** Parental stress and feelings of sorrow and grief may result as well ***(Hobdell et al., 2007).***

Typical parental responses are shock, devastation, anger, frustration, sorrow and depression. Witnessing a seizure in one's young child, especially a tonic-clonic seizure, can be one of the most anxiety-provoking experiences for a parent. It usually leads to feelings of helplessness and fear and often results in overprotection or overindulgence of the child. Parents often fear divulging their child's epilepsy to their friends and relatives because they experience a sense of shame, self-blame and rejection. They consequently withdraw from their relatives and social circle. Mothers may fear that the child's epilepsy is due to neglect during

pregnancy. Feelings of guilt and inadequacy develop, leading to further loss of self-esteem. Due to their anxious withdrawal from others, parents risk increasing isolation and loss of social support ***(Spangenberg & Lalkhen, 2006).***

After the initial perplexity and shock, according to some researchers, some parents experience a strong urge to protect, while others remain uncertain and confused about their emotions, fearing emotional investment in a person who may bring them more sorrow than joy. Some parents show initial reluctance in their contact with their child, either through true incapacity to relate to an abnormal child, or through fear of triggering an epileptic seizure ***(Pontes et al., 2006).***

Some parents find the diagnosis a relief, while others completely deny the news or wonder what they have done to suffer so much. Parents generally show a great need to understand the cause of the problem, seeking tirelessly to find a justification as a way of apportioning blame, either to themselves, to their partners, or, as is common, to the health care team accompanying the child ***(Pontes et al., 2006).*** Maladaptive perceptions may then develop in response to a medical condition such as epilepsy based on parents' cognitive and psychosocial resources, and these maladaptive perceptions may then impact the patient's outcome ***(Hobdell et al., 2007).***

Sixty seven parents of epileptic children completed brief questionnaires about their sorrow and coping styles. Results demonstrated chronic sorrow as measured by the Adapted Burke Questionnaire (10.45±7.9). Interestingly, the total score was not significantly different between parents of children with refractory and non-refractory epilepsy or parents of children with comorbid or without comorbid conditions. Selection of the individual item "*disbelief*", however, was significantly increased in parents of children with non-refractory epilepsy, and selection of the item "*anger*" was significantly increased in parents of children with comorbid conditions. Parental coping styles were similar to those reported in the normative data for the instrument used, the Coping Health Inventory for Parents (CHIP) ***(Hobdell et al., 2007).***

As the child grows older, parental stress is likely to increase due to management difficulties, financial demands and increased concern about the child's future. The addition of behavioral problems, a common occurrence in adolescents with epilepsy, may further increase stress and burden ***(Spangenberg & Lalkhen, 2006).*** It was found that parents of epileptic children generally were more stressed, had lower self-esteem, and experienced more emotional problems ***(Camfield et al., 2001)***

Diagnosis of epilepsy in their child leads to stress in parents. Focus by parents on the child with epilepsy can result in poor relationships between the child with epilepsy

and siblings and psychological difficulties among siblings ***(Hills, 2007).*** Siblings of children with chronic epilepsy also have increased behavioral issues, mostly in externalizing behaviors. Siblings of CWE report higher level of concern (1) that people will make fun of them because of their sibling's seizures; (2) not knowing how to help during a seizure; (3) feeling left out; and (4) regarding- injury and death as a result of a seizure ***(Ronan et al., 2003).*** Such focus can also affect family cohesion and relations between the family and their community. It can result in the people with epilepsy growing up to make a poor parent themselves ***(Hills, 2007).***

Family risk factors have an enduring impact on behavioral problems in CWE throughout the course of epilepsy. In children with new-onset epilepsy preexisting family problems and off-balance parenting after the diagnosis of epilepsy were stronger predictors of behavioral problems than epilepsy-related variables ***(Oostrom et al., 2003).*** Furthermore, poor family mastery and insufficient parental confidence in establishing discipline have moderating effects on the child behavioral problems at the onset of epilepsy and 2 years later ***(Austin et al., 2004).***

Childhood epilepsy impacts on the entire family, because the demands for change and the use of family resources increase. This may lead to an increase in family stress and disruption. A chronic illness with unpredictable characteristics like epilepsy puts a family at risk for poor communication, poor cohesiveness and poor integration. The

burden of care may fall more heavily on one member, which may lead to resentment and increased family tension. Plans for the future are often placed on hold. The family may spend less time enjoying activities outside the home, fearing that the child may have a seizure, and inviting friends to the home may come to an end ***(Ellis et al., 2000).***

One parent may have to end his/her employment outside the home to take care of the child, which may lead to a reduced income for the family and therefore the reduction of pleasurable activities. Having a child with epilepsy incurs many expenses, since specialist consultations, medication and special investigations are costly. For parents who live in rural areas, transport to and from the hospital or medical centre and the cost of child care for the children left at home bring additional expenses ***(Spangenberg & Lalkhen, 2006).***

Poor family adaptation to epilepsy and parental rejection of the child predicted internalizing, attention problems in children with chronic epilepsy. Overcontrolling parenting was associated with higher levels of behavioral problems, particularly internalizing problems in CWE. Mother-adolescent relationship problems were significant predictors of impaired psychosocial adjustment in adolescence above and beyond their seizure status ***(Plioplys et al., 2007).***

Coping has been defined as dealing with and attempting to overcome difficulties. Various components of

coping may include problem-focused strategies and cognitive and emotion focused solutions, including wishful thinking and avoidance. The former are deemed more positive, while the latter are felt to be more negative or unhelpful ***(Hobdell et al., 2007).*** In parents of children with epilepsy, effective problem-solving coping strategies as opposed to avoidant coping strategies should likewise help to diminish psychological distress. Parents who feel able to handle their child's illness and who feel that they have the necessary skills to deal effectively with seizures, experience less burden and stress ***(Schumacher et al., 2000).***

***Roles and responsibilities of parents of children with epilepsy:***

The most basic role of parents is to provide a safe psychological and physical environment from which the child can explore the world and master the developmental tasks of childhood and adolescence. The unsuccessful negotiation of the stressors attached to epilepsy prevents the child from adapting successfully to his/her condition and hampers normal personality development. This leads to psychosocial adjustment problems throughout childhood, continuing into adulthood ***(Austin, 2001).*** Parents play the most significant role in helping the child with epilepsy adapt to his/her condition. In practical terms their functions include seeking treatment, ensuring the child's compliance with treatment, facilitating the child's functioning in and

outside the home, and regulating the impact of other people's attitudes on the child ***(Ziegler et al., 2000).***

The nature of parents' roles changes during the course of the child's developmental stages. During infancy and early childhood children need an environment where they can develop autonomy and initiative. If parents' response to the diagnosis of epilepsy is overprotection and overindulgence, the child is deprived of experiencing feelings of competence and developing life skills ***(Austin, 2001).***

The developmental tasks of middle childhood include becoming more independent of parents and more attached to peers. During this stage it is crucial for the child's psychosocial development to be actively involved in peer groups and to achieve success in the school environment. Epilepsy can interfere with these tasks. Unless the parents' attitude is positive, constructive and empowering, the child will feel different from peers, withdraw from peer groups and develop poor self-esteem ***(Ziegler et al., 2000).***

Adolescence is the period during which the child's identity as an individual in his/her own right should be consolidated. Achieving independence from parents, establishing healthy interpersonal relationships outside the family and choosing a vocation are essential developmental tasks of adolescence ***(Ziegler et al., 2000).*** Overprotection may result in failure to develop a sense of self-competence,

which in turn leads to poor self-esteem and a self-perception of being "different". Seizures and having to take anti-epileptic medication may lead to a sense of physical incompetence. An adolescent with epilepsy may withdraw, become depressed or display behavior problems in response to his/her condition. In each of the three above-mentioned developmental stages, constructive parental responses to the child's condition are crucial to successful mastery of developmental tasks ***(Spangenberg & Lalkhen, 2006).***

Given the above, it is clear that a diagnosis of epilepsy involves a complex array of factors that influence its treatment and clinical course. Clinicians should consider that the patient is a human being who has a complex biological organization with important psychological characteristics. This can influence the therapeutic response: we must treat the epilepsy, but it is more important to treat the epileptic. Interventions geared not only to medical therapy but also aiming at coping strategies, education and rehabilitation, working both with the patient and the family, are therefore fundamental. ***(Pontes et al., 2006).***

***<u>Health related quality of life (HRQL) in CWE:</u>***

The concept of health related quality of life (HRQL) does not directly evaluate psychopathology, but instead a patient's self-perceptions of well-being in the physical, mental, and social domains of life ***(Lach et al., 2006).*** In the past decade significant progress in health related quality of

life (HRQL) research has been achieved in adults with epilepsy. New scales have received acceptance as important tools to evaluate the well-being of people with epilepsy in the clinical setting, in judging the benefit of epilepsy surgery, and in the evaluation of novel antiepileptic drugs. The most likely reason that similar research has not included children with epilepsy is the potential conceptual and operational difficulties in developing HRQL measures for them, and possibly problems in completing forms, rather than the notion that such scales are less necessary or important for them ***(Ronen et al., 1999).***

CWE are found to have relatively more compromised health-related quality of life (HRQL) in the psychological, social and school domains compared to children with asthma, suggesting that these problems are specific to epilepsy and not simply the result of living with a chronic condition ***(Ronen et al., 2003).*** Despite evidence that poor HRQL in childhood may negatively affect psychosocial functioning and outcome in adulthood; there have been no studies to date on the association with measures of psychopathology in CWE ***(Plioplys et al., 2007).***

Quality of life for children with epilepsy is dependant on multiple factors including developmental level, seizure type and frequency and the way in which the child with epilepsy has been treated by family and others. The temporary loss of control induced by a seizure poses

different levels of problems for the growing child who is striving to attain autonomy. Adolescents, in particular, have difficulty coping with the unpredictable nature of seizures and the restrictions that epilepsy may place on socially desirable goals that come with maturity, such as driving and occupational choices ***(Leonard & George, 1999).***

Although epilepsy is a medical condition, the person with epilepsy also has to cope with its psychological and social consequences ***(Hills, 2007).*** Social isolation and withdrawal are commonly reported stressors affecting adjustment of children with epilepsy. Repeated hospitalizations may interfere with opportunities for social interaction and contribute to feelings of social isolation. Lack of self-esteem reinforces this pattern, reducing the child's opportunity to learn appropriate social skills ***(Leonard & George, 1999).***

CWE adjustment to illness and their HRQL is affected by the experience of stigma, which may lead to poor self-esteem, rejection by peers, avoidance of age-appropriate activities, and social isolation. CWE are more secretive and ashamed about their condition than are children with other chronic illnesses. Due to fear of stigma, parents and teachers may have lower expectations of children or limit their developmentally appropriate activities. In addition, parents who think that their child will be stigmatized and who perceive that epilepsy limits their child report more child behavioral problems than parents who do not share these

perceptions. Stigma, therefore, may contribute to the development of adjustment problems and mood disorders in CWE ***(Plioplys et al., 2007).***

Lower self-esteem can result from perception of the self as less competent than others and self-categorization as an "epileptic" and consequent perception of stigma. Epilepsy is a "hidden" or "invisible" disability, as no symptoms are apparent except during a seizure. It often has no apparent cause, which results in a fear of the unknown. Social isolation and poor social adaptation can result from perceived stigma or over-dependency caused by parental overprotection. The people with epilepsy also often fears embarrassment by a seizure, causing reluctance to engage in social interaction, with concomitantly low self-esteem and academic under-achievement ***(Hills, 2007).***

In practical terms, the stigma associated with epilepsy, and the insensitivity of others, are also stressors that affect the emotional and adaptive behavioral responses in these children. It is their experience that many of the children with whom they come in contact are excluded from activities with classmates; teased and bullied; and sometimes suspended from school because of behavioral issues. These factors further reinforce the child's negative view of him/herself and alienate the child from the usual social and learning experiences that promote self-esteem and normal social development ***(Elliot et al., 2004).***

In Ronen et al. study, the focus group of children seemed distressed mostly about daily life restrictions. Their loss of independence was considered as a severe and saddening hardship. The children were also very concerned about how they were perceived and treated by their peers. Furthermore, they were uneasy about how their seizures were going to be handled by outsiders and were bothered by adverse effects of medication ***(Ronen et al., 1999).***

To generate a comprehensive list of the HRQL elements organized into categories and subcategories we should consider the following:

- ***The experience of epilepsy:***

This includes the entire context, settings, and situations of coming to terms with and understanding epilepsy. These include the discovery of having epilepsy, how seizures feel, knowledge of epilepsy, nature of the seizures, feeling trapped by the condition, keeping it as a secret, and the various emotional aspects associated with having epilepsy.

- ***Life fulfillment and time use:***

This includes practical issues in day-to-day activities, such as school issues, recreation, home activities, safety, future, and health-care issues that are affected by epilepsy.

- ***Social issues:***

These include the internal and external social consequences of epilepsy, such as loss of independence, stigma, support, and relationships among family members and peers.

- ***Impact of epilepsy:***

This includes personal and psychological impacts, such as self-concept, feeling of uncertainty, seeing oneself as different, limitation of activities, as well as cognitive and physical impacts.

- ***Attribution:***

This includes explanatory issues, how many and what burdens or concerns are truly related to epilepsy, or rather affected by the child's development, or by health or social problems.

The different codes were categorized according to these themes *(Table 4)*. While interpreting the transcription of parents' and children's comments they often found rich, meaningful, and representative statements which provided a deeper illustrative understanding of the burdens and concerns of the children; examples are given next to the appropriate domains ***(Ronen et al., 1999).***

**Table (4): The HRQL components in childhood epilepsy *(Ronen et al., 1999)***

| *Domains* | *Sample quotations* |
|---|---|
| ***Theme 1*- Experience of epilepsy** | |
| • Discovery | C: 'My mom, she thought I was ignoring her, but I was really staring into space. They had a test done on me and that's how I found out.' |
| • Child's description | C: A seizure 'it feels like every bone in your body stops.' |
| • Feeling trapped/ epilepsy always there | C: 'I can't even pick it up (the epilepsy), that's always there, how big it is, how big a problem.' |
| • Child's knowledge | P: 'She doesn't know she has epilepsy, by that word. |

| | |
|---|---|
| | We call it twitching because I was afraid to say epilepsy because there is a stigma. I feel and I think they would say "well you can't come to a birthday party because it's swimming", that kind of thing.' |
| • *Nature of the seizures*<br>o Timing of seizures, frequency, severity location, after effects, seizure control<br><br>o Handling of seizure situation by others, other people's under-standing | C: 'My seizures are like a tingling and fuzzy feeling and I still know what I'm doing, I just can't talk and that doesn't mean when I get older that I'll crash the car if I'm driving.'<br><br>C: 'I had a seizure on the playground and they all ran away and I just sat down and I was sitting here until school ended and I didn't know what to do.' |
| • *Medication issues*<br>o Interrupting activities, management issues, feeling different due to medication<br><br>o Adverse effects, cosmetic issues | C: 'I really don't want to take my pills, that's why it's a big problem.'<br><br>C: 'The medicine helps you. Sometimes the medicine isn't nice, (because of) the side effects that come with it. I get tired.' |
| • Cognitive experiences | P: 'She did at one point think that she was actually stupid. That was the word, the terminology she used, I'm stupid. Because she used to be so good at math, she used to be so good at everything.' |
| • Epilepsy as our secret | C: 'Sometimes if you have friends, and you tell them (you have epilepsy), they won't be your friend anymore.' |
| • *Emotional experiences of epilepsy*<br><br>o Child's affect<br><br>o Child/parent fear | <br><br>P: 'He goes through depression stages where he wishes he was dead. Like, he'll tell you, "I wish I was dead." Like my life isn't that great, my life is not perfect.'<br><br>P: 'As far as the fear of having a seizure she has closed off ...she will not go on school trips. She's afraid. She's closed off all her relationships with her friends. I'm weird, I'm stupid. I don't know what's happening." |

| | |
|---|---|
| o Child/parent hope | C: Wish: 'to be a millionaire and let the doctors find a cure for epilepsy.' |
| **Theme II – <u>Life fulfillment/time use</u>** | |
| • Home activities | P: 'If she's just around home playing with friends or being with family it doesn't really have a big impact on her at all. But when she goes to school or does other activities that's when it has an impact on her.' |
| • School issues and activities | C: 'Like my teacher, she thinks I'm a crash dummy because sometimes I have these little seizures and I just slip on some ice and I keep on falling down. It happens almost every day so they call me crash dummy.' |
| • Recreation | P: 'And then after we found out what it was, he was told he couldn't (scuba) dive so he was a little upset over that because we go on holidays every year and he sits out and we all go (scuba) diving.' |
| • Safety | C: 'I feel the safest at home |
| • Future | C: 'I'll have it for a long time. It's not something that you can give away.' |
| • Hospital and health-care issues | P: 'He was more upset with all the testing and having to go through the blood work and he had to have a double CT scan. They had to put the dye in and he was more upset about the testing than he was actually (about) having epilepsy.' |
| **<u>Theme III – Social issues</u>** | |
| • Carrying on with life | C: 'I feel like I live a normal life except sometimes I have, like, a seizure. It's just like someone falling off their bike, almost.' |
| • Child's independence | C: 'I can't have a bath on my own; I can't go swimming on my own. I have to have somebody watching me.' |

| | |
|---|---|
| • Social experience<br>o Teasing and bullying<br>o Stigma<br>o Isolation<br>o Support | C: 'Friends...sometimes they would call me "stupid, get away, loser".'<br>P: 'I find a lot of people call her retarded. And that's what she doesn't like.'<br>C: 'They treat me different, they like, they ignore me sometimes.<br>P: 'When my daughter took a seizure at school, all the kids pulled together.' |
| • Peer relationships | C: 'And he (a friend) says "why don't I hit you in the head and then you are going to go into a seizure?"' |
| • Family<br>o Parent-child relations/interactions<br>o Siblings | C: 'My mom gets scared when I have seizures'<br>P: 'And my older children are very embarrassed of her right now because she is on a higher dosage. They go what's wrong with her? Don't put her near our friends. She acts so kooky.' |
| • Secondary gains/benefits | C: 'Well, the medicine I take doesn't taste good but the one thing I like about it is my mom always goes out and buys ice cream so whenever I have it I always get ice cream to take with it.' |
| **<u>Theme IV – Impact of epilepsy</u>** | |
| Physical impact | C: 'Sometimes I don't feel good and after school I feel sleepy.' |
| Personality, self-concept | P: 'Lack of confidence I think is the biggest part of having epilepsy for them because they don't feel positive about themselves a lot of times.' |
| Uncertainty | P: 'She hopes that one day she won't have the problem, but you don't know that for sure.' |
| Seeing oneself as different | C: 'It feels like nobody's like, everybody's like way different than you, like everybody looks alike and |

| | |
|---|---|
| | you're the only person in the world that's different. That's what it feels like.' |
| Understanding of others' disabilities | P: 'I think because the kids do have a problem, and it is a medical problem, whether it is mental or physical, I think that enlightens them a lot.' |
| Cognitive impact | C: 'At school, they used to call me stupid and dumb because I had done (repeatedly) the same things and I then wouldn't know it.' |
| Limitations of activities | C: 'I can't do as much now. I can't go swimming by myself. I have to have someone on my porch.' |
| **Theme V – Attribution** | |
| | P: 'I think that's what's so frustrating about it. You don't know whether it's the child's personality, the medication, or the condition that makes them the way they are.' |
| Epilepsy vs child development | P: 'I don't think the epilepsy is playing down into her overall quality of life as much as is growing up is.' |
| Epilepsy vs other health | P: 'She has asthma as well, so I feel I need to check if she needs her puffers. The asthma has something to do with how I treat her as well.' |
| Epilepsy vs social issues | P: 'Everybody hated her and all this kind of thing and I phoned the vice principal and I said "does something happen when they get to Grade 4?", and she said they turn nasty.' |

Support within existing social networks, and meeting informally with other families with similar predicaments, are potentially very appropriate interventions for a community based setting in developing countries. Pal and colleagues illustrate that effective interventions with innovative use of existing community resources could improve the HRQL and the psychosocial outcome in CWE, and that these interventions can be inexpensive and therefore suitable for developing world societies ***(Ronan et al., 2003).***

Participation in physical activities and social engagement with peers is particularly important during childhood development. During conversations with families of children with epilepsy, researchers frequently hear that seizures, and the associated secondary problems, often exclude children from full participation in academic, recreational and social experiences. Concern for the child's safety may lead to restriction of normal school activities, which most children take for granted. This increases the child's sense of social isolation. Isolation from these important social learning experiences further enhances a negative perception of self, informing the child, that he or she is 'not normal' at time in life when being 'normal', not 'different' is highly valued. It is important that parents advocate for extra support in the school to facilitate the child's participation in school activities (e.g. playground, gym) that facilitate interactions with other children. Involvement in school activities is paramount to fostering a sense of emotional well-being well as, promoting social and physical development ***(Elliot et al., 2004).*** The role of schoolteachers is important, so it might be necessary to strengthen education on epilepsy and behavioral disturbances in the training curriculum for schoolteachers and to add such topics to postgraduate training ***(Hanai, 1996).***

Accurate recognition of emotions is necessary for appropriate human social interaction ***(Fowler et al., 2006).*** Clinically, emotion perception deficits may be relevant in

that the ability to recognize facial expressions in others is an important social skill that is crucial for complex interpersonal interactions and that may be important in order to infer what others think, feel or what their intentions might be ***(Ammerlaan et al., 2008).*** The amygdala plays an important role in our ability to recognize emotions in others, and processing emotional memories and evaluating social cues. Human clinical studies have shown that impairments in recognition of facial expression occur when there is bilateral damage to the amygdala and that recognition of fear is particularly severely affected ***(Fowler et al., 2006).***

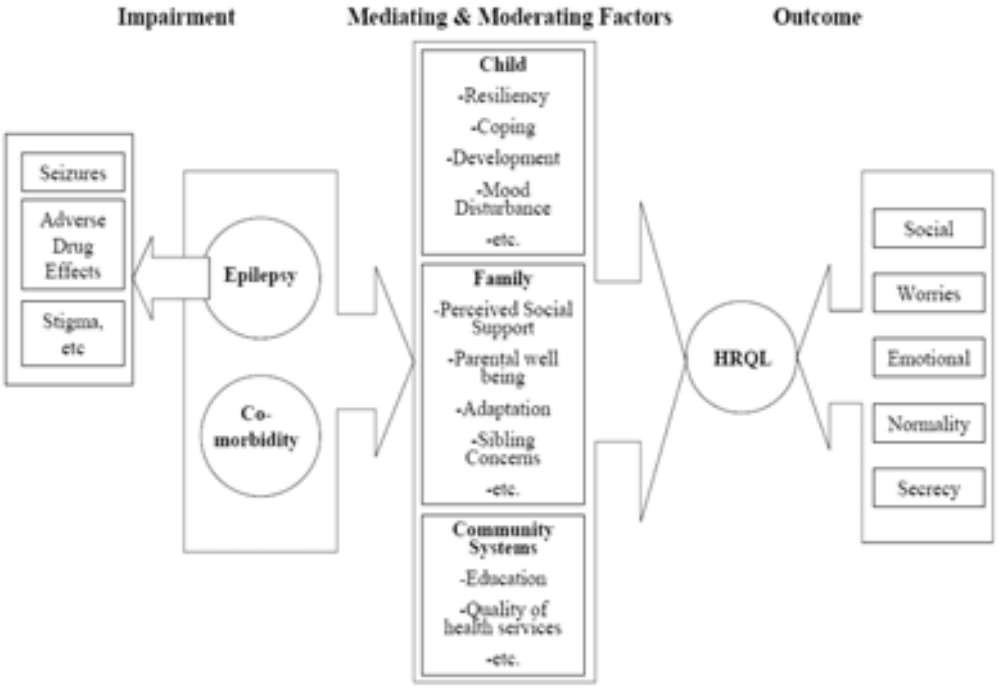
Patients with temporal lobe epilepsy (TLE) have higher incidence of emotional, behavioral, cognitive, and, consequently, social difficulties than in the general population. These social difficulties may be externally driven in part by stigmatization and public discrimination of epilepsy. However, it is hypothesized that damage to the amygdala and associated impairments in recognition of others' emotions may also contribute to social difficulties ***(Fowler et al., 2006).***

Despite recent achievements in developing HRQL measures, there is a need to improve our understanding of the functional and experiential dimensions associated with complex neuro-developmental disorders. It is difficult to attribute better or poorer quality of life to the nature of epilepsy alone, when so many disparate factors play key roles in people's lives. These factors include, among others, a

child's resilience, co-morbid conditions, parental well-being, family factors, attitudes and societal/cultural variables *(Figure 3)*. Recent studies have shown that relationships between clinical symptoms such as seizure frequency and severity, or other biomedical markers, have only moderate correlations with HRQL. Furthermore, HRQL may change over time with the development of the child and the family's accommodation to the situation. In addition, we need to learn what truly encompasses comprehensive patient care, define the goals of management, and attempt to evaluate the impact of interventions wherever possible ***(Ronan et al., 2003).***

A comprehensive assessment needs to be carried out on a regular basis to facilitate early identification of psychiatric issues, social problems and referral for the rehabilitation services whenever required. In case of children with epilepsy, family therapy may be needed to unravel and improve complicated family dynamics in order to optimize the quality of life in both patients and parents along with other siblings ***(Raguraman & Wadoo, 2006).***

**Figure (3): Conceptual model of quality of life in childhood epilepsy *(Ronen et al., 2003)***




Education should be a standard part of all treatment for pediatric epilepsy patients, particularly those at risk for comorbid psychiatric and behavioral problems. This includes informing parents about exactly what they may expect to happen in the course of the child's illness, teaching them how to manage the symptoms of epilepsy, explaining how to handle the medication, and identifying symptoms they should watch for in their children. Instructing parents and children with epilepsy about epilepsy and providing training in coping techniques, decision making, and communication,

improved knowledge, self-perceived social competency, and behavior ***(Dunn & Austin, 2004).***

Social skill programs and rehabilitation are also need to be provided, particularly in children. Psychological counseling in children with epilepsy should include all aspects of self and environmental issues. Undue restriction and withdrawal from social life are better managed through psychosocial concern and special educational process ***(Raguraman & Wadoo, 2006).***

Contributions to the child's development have to do with motivation to learn, leisure activities, stimulation, dietary and personal hygiene exercises, which are aspects worked on through the assessment of the patient's resources and potential, thus helping rebuild the interrupted or non-existent daily life, turning situations into meaningful experiences that can somehow contribute the child's social integration ***(Pontes et al., 2006).*** If psychotherapy proves ineffective, psychopharmacology is often effective ***(Dunn & Austin, 2004).***

Comprehensive treatment programs for children with epilepsy should include thorough evaluation of epileptic events, response to various treatment modalities, academic and psychosocial interventions. The interaction between learning, behavior, social and cognitive problems are multi-factorial and multi-determined and are the consequence of seizures and their treatment effects, which are presently

incompletely understood. As with all chronic disorders, epilepsy requires adjustment by the child, family and society. Some aspects of epilepsy cannot presently be altered, no matter how well they are currently understood or accepted. The complexity of chronic epilepsy necessitates a multidisciplinary and multimodal approach to evaluation, treatment and intervention. It is through collaboration of professionals from the disciplines of medicine, education, community advocacy and intervention, combined with family support and involvement that one will continue to make progress in treating epilepsy ***(Leonard & George, 1999).***

# ***Discussion***

Childhood epilepsy is a biologically based risk factor for child and adolescent psychopathology and family adjustment problems. In the last decades, researchers assisted to an increased interest in research in this field mainly due to recent development of specific measurement instruments in child psychiatry and the improving knowledge about neuro-development illness factors ***(Otero, 2009).***

Although narrative reviews have confirmed the high prevalence of psychopathology in children with epilepsy ***(Kim, 1991; Leonard & George, 1999; Besag, 2002; Dunn, 2003)***, it is difficult to ascertain which particular problems are most common and how severe these problems are among children with epilepsy ***(Rodenburg et al., 2005b).***

Although psychiatric disorders are frequent in epileptic patients, they are not frequently diagnosed and treated ***(Ott et al., 2003; Caplan et al., 2005).*** It was found that only one third of the patients with psychiatric disorders receive treatment ***(Ott et al., 2003).*** The diagnosis and treatment rate can be expected to be lower in Egypt's conditions where families are reluctant to seek psychiatric help. This situation makes controlling psychiatric disorders in epileptic patients more difficult.

Therefore the present study was specifically designed to investigate the rate of psychiatric disorders and cognitive impairment among epileptic children. The

interest of our study is to reveal what are the most prevailing psychiatric disorders among the study sample, the pattern of cognitive impairment, and to what extent seizure related variables affect both behavioral and cognitive problems.

## Psychopathology among epileptic children and adolescents:

Interictal behavioral changes in epilepsy remain controversial and difficult to define, mainly because most epidemiological studies have been carried out in centers for epilepsy, in which many patients have refractory epilepsy and a variety of pathological conditions ***(Torta and Keller, 1999).*** Behavioral disorders may precede, occur with, or follow a diagnosis of epilepsy and differ between children and adults. Specific childhood co-morbidities include attention-deficit hyperactivity disorder (ADHD). Some co-morbidities, like depression and anxiety, are present both in children and adults with epilepsy. Serious psychiatric disorders as psychotic disorders are less common in children than adults with epilepsy ***(Pellock, 2004).*** Most behavioral disturbances are observed more frequently in people with drug-resistant epilepsy, frequent seizures, and temporal lobe epilepsy ***(Gaitatzis et al., 2004).***

The classic community study of neuropsychiatric disorders of ***Rutter et al. (1976)*** found that (33%) of children with epilepsy have psychiatric disorders in

comparison to a rate of (6.6%) in the general population of children, but they did not specifically delineate disorders.

Our results confirmed some previously reported studies, as we found that 48.33% (n=58) were suffering from psychiatric illnesses. Moreover, we found that the patients with focal seizures were suffering from psychiatric illnesses by (57.83%), while patients with generalized seizures were suffering from psychiatric illnesses by (39.34%) *(Table 9 & Figure 8).*

These findings were similar to a large study done by ***Hoare (1984)***, who studied two groups of epileptic children, one newly diagnosed and one with chronic epilepsy, were compared with two comparable groups of diabetic children and with children in the general population in order to investigate the development of psychiatric disorder. Psychiatric disturbance was based on parent report on a well-established behavior questionnaire. The results confirm previous findings that children with chronic epilepsy are significantly more disturbed than children with chronic physical illness not involving the central nervous system, and than children in the general population. Children with newly diagnosed epilepsy were also significantly more disturbed than those with newly diagnosed diabetes, and than children in the general population. The rate of psychiatric disturbance was similar in the two groups of epileptic children, with (45%) of those in the new-onset and (48%) of those in the chronic epilepsy group showing evidence of psychiatric disturbance, yet he did not determine rates of specific disorders. In both

groups of epileptic children, those with focal EEG abnormalities and/or complex partial seizures were particularly vulnerable to psychiatric disturbance.

In our study we found 15% (n=18) suffered from ADHD, 5% (n=6) suffered from conduct disorder, while 0.83% (n=1) suffered from oppositional defiant disorder. Also, we found depression in 3.33% (n=4), hypomania in 0.83% (n=1), social anxiety disorder in 5.83% (n=7), specific phobias in 3.33% (n=4), generalized anxiety disorder in 1.67% (n=2), separation anxiety in 0.83% (n=1), while adjustment disorder was in 0.83% (n=1). Co-morbid disorders presented (10%), the most common diagnoses were ADHD and conduct disorder in 5.83% (n=7), followed by ADHD and specific phobia in 1.67% (n=2), the same was for depression and generalized anxiety disorder in 1.67% (n=2), while depression and social anxiety disorder presented only 0.83% (n=1) of the sample *(Table 10 & Figure 9).*

***El-Gamal et al. (1996)*** conducted a research to study psychiatric aspects and cognitive functions among children (8-14 years old) with temporal lobe epilepsy, together with diagnosing the patients according to DSM-IV criteria. They found psychiatric diagnoses in (63.63%) of the sample, with ADHD (24.24%) as the most prevailing diagnosis, while conduct disorder presented only (1.51%) of the patients.

***Caplan et al. (1998)*** administered structured psychiatric interviews to 60 children with complex partial

seizure disorder (CPS), 40 children with primary generalized epilepsy with absences (PGE), and 48 control children, aged 5 to 16 years. Significantly more patients with epilepsy had psychiatric diagnoses compared with the control children.

***Caplan et al. (1998)*** reported that (63%) of the children with complex partial seizures and (55%) of the children with primary generalized epilepsy with absences had significantly increased frequencies of psychiatric diagnoses as compared with controls. Unlike our study that revealed more psychiatric illnesses among patients with focal seizures, they found no statistically significant differences in the distribution of the following psychiatric diagnoses in the patients with CPS and PGE: (25%) of children with CPS and (26%) of children with PGE had disruptive disorders (i.e. attention deficit-hyperactivity disorder, oppositional defiant disorder, conduct disorder). They found that (13%) of the patients with CPS and PGE had anxiety/affective disorder, and (14%) of the children with CPS and (16%) of the children with PGE had comorbid disruptive and anxiety/affective disorders.

On the other hand ***Austin et al. (2001)*** studied a sample of 224 children (4–14 years old) with a first recognized seizure and their 135 healthy siblings. Behavior problems were measured using the Child Behavior Checklist (CBCL). Higher than expected rates of behavior problems were found in the total seizure sample, with rates of (32.1%) to (39.5%).

The authors followed up 224 children with new-onset seizures over a 24-month period. The Child Behavior Checklist (CBCL) was administered to measure behavior problems. They found that (55-58%) of the children with recurrent seizures had behavioral problems. Epileptic syndrome/seizure type was not a significant predictor of behavior problems ***(Austin et al., 2002).***

***Davies et al. (2003)*** performed the first epidemiological study that directly measured emotional and behavioral impairments that epileptic children experience. Information was obtained by interviewing a main carer and teacher for 10 316 children; 67 children with epilepsy were identified, and compared with the 47 children with diabetes, and 10 202 controls. DSM-IV psychiatric diagnoses were derived from the Development and Well-Being Assessment in combination with the interview and a specialist clinician rating. Parental reports of emotional and behavioral problems, their impact, and associated peer problems were also obtained. Rates of psychiatric disorder were (37%) in epilepsy, (11%) in diabetes, and (9%) in control children. Parents of children with epilepsy consistently reported more problems, with greater impact and associated peer problems. They did not have the statistical power or clinical information in this study to establish whether the risk of psychiatric disorder varied with characteristics of the epilepsy, such as seizure frequency, type, or length of illness, which is inconsistent with our findings that seizure frequency associated with higher rates of psychiatric disorders.

Parents' and teachers' perceptions of the children's behavioral problems were quantified in ***Oostrom et al. (2003)*** by using the Total Problem score of the Child Behavior Checklist (CBCL) and the Teacher's Report Form (TRF). Questionnaires were filled out immediately after diagnosis and 3 and 12 months later. Children with epilepsy have more behavioral problems than do healthy classmates. No adverse effect of antiepileptic drug (AED) treatment was found. Although the percentages of patients with clinically relevant behavioral problems are consistently (25%) by parents and (22%) by teachers, at each assessment, different children contribute to these percentages. They found that: (a) Behavioral problems are common in epilepsy, but are not persistent. (b) Behavioral problems are perceived to occur already in the earliest stage of the disease.

***Ott et al. (2001)*** investigation examined psychopathology in 48 children with complex partial seizures (CPS), 39 children with primary generalized epilepsy with absence (PGE), and 59 non epileptic children, aged 5 to 16 years, who were recruited from both community and tertiary pediatric neurology clinics. They compared the three groups regarding the Child Behavior Checklist (CBCL) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). The CBCL identified psychopathology in (26%) and the K-SADS in (51%) of the CPS and PGE patients. The CPS and PGE groups had significantly higher mean CBCL scores, as well as higher rates of psychiatric diagnoses and symptoms of psychopathology, compared with the non-

epileptic group. However, the CPS and PGE groups did not differ in these measures. They reported depression in (12%) and anxiety in (13%) of the sample.

***Ott et al. (2003)*** used The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), the Child Behavior Checklist, the Test of Language Development, and the Wechsler Intelligence Scale for Children–Revised (WISC-R) to evaluate 114 children, aged 5 to 16 years, with either complex partial seizures (CPS) or primary generalized with absence (PGE, petit mal). They found that (60%) of the subjects had a DSM-IV psychiatric diagnosis. They found (15.9%) of the sample were diagnosed as affective/anxiety disorders, (23%) as disruptive behavior disorders, (21.2%) as co-morbid disorders.

***Thomé-Souza et al. (2004)*** found that depression occurred in (36.4%) and attention-deficit hyperactivity disorder (ADHD) in (29.1%), these being the most frequent psychiatric disorders in their sample. Focal epilepsy was significantly more frequent in children and adolescents with psychiatric disorders. Their findings were similar in the rates of ADHD (22.5%), while rates of depression was much higher than ours. Yet, our finding that the focal epilepsy was significantly more frequent in children and adolescents with psychiatric disorders, confirmed their finding of the same phenomenon.

***Caplan et al. (2005)*** studied a sample of 171 epilepsy patients, 100 children with complex partial seizures, 71

children with childhood absence epilepsy of average IQ. They used parent reported instruments, and found anxiety disorders as a sole diagnosis in (35%), anxiety disorders co-morbid with disruptive disorders in (28%), depression as a sole diagnosis presented only (5%), depression co-morbid with disruptive disorders in (14%). Co-morbidity between anxiety and depression presented (3.5%), while co-morbidity between anxiety, depression and disruptive disorders presented (14%) of the whole sample. These rates are much more than we found in our sample *(Table & Figure 6)*, this may be due to difference in study design, variations in selection of patients studied and differences in classification of seizure types.

While ***Bilgiç et al. (2006)*** used MINI, studied 30 children aged 8-16 who attended a children's neurology clinic found psychiatric disorders in (26.7%) of epileptic patients, in terms of DSM-IV criteria, which is much lower than the (48.33%) that we had in our study, this may be due to different sample size.

***Freilinger et al. (2006)*** used The Child Behavior Checklist (CBCL) to assess parent-reported behavioral and emotional problems in 108 5 to 18 years old children with various epilepsy syndromes. Specific medical epilepsy-related factors, such as etiology, age at onset, seizure symptoms, prognosis, seizure frequency, electroencephalography (EEG), and anticonvulsive therapy, were recorded during a regular follow-up examination, (22.2%) of their patients showed moderate to severe behavioral or

emotional problems as measured by the Child Behavior Checklist total score.

This wide range reflects methodologic differences, such as differences in type of diagnostic instruments (e.g. structured psychiatric interviews, self-report scales), number and type of informants (e.g. child, parent, teacher), diagnostic end points (e.g. DSM-IV diagnosis, borderline/clinical scores), age range of subjects (e.g. children, adolescents), recruitment sources (e.g. community samples, university affiliated clinics), chronicity of study samples (e.g. new onset seizures, chronic epilepsy), and sample size ***(Caplan et al., 2005).***

Higher prevalence of psychiatric disorders with epilepsy could be explained by the hypothesis that epilepsy and abnormal behavior may be different aspects of the same pathological event. Many children and adults have behavioral problems, even if they are seizure-free. These findings are consistent with the hypothesis that in some patients epilepsy is a pervasive condition including both seizures and behavioral problems ***(Cornaggia et al., 2006).***

***ADHD & Disruptive behavior disorders:***

Attention-deficit–hyperactivity disorder (ADHD) has been associated with childhood epilepsy; prevalence figures have ranged from (8%) to (77%), depending on the sample studied and the criteria used for diagnosis. These findings would suggest that disorders of attention may be the most frequent behavioral problems in children with

epilepsy ***(Dunn et al., 2003).*** These findings are in agreement with ours, as we had 15% (n=18) of the sample diagnosed as ADHD, while ADHD and conduct disorder presented 5.83% (n=7), and ADHD and specific phobia in 1.67% (n=2).

Attention deficits are more prevalent in children and adolescents with epilepsy than in those affected with other chronic illness, and are likely related to brain damage ***(Otero, 2009).***

Several studies have reported on ADHD symptoms and epilepsy without standardized measures. ***Holdsworth and Whitmore (1974)*** found that teachers noted inattention in (42%) of children with seizures. Children with epilepsy and impaired school achievement more often had inattention (59%) compared with children with seizures and average or better achievement (20%).

ADHD affects three to five times more children with epilepsy compared with general population. Five studies that used clinical samples and DSM-IV-based criteria for ADHD found symptoms of ADHD in (14%) to (38%) of children with epilepsy ***(Caplan et al., 1998; Semrud-Clikeman and Wical, 1999; Dunn et al., 2003; Ott et al., 2003; Thomé-Souza et al., 2004).***

***Semrud-Clikeman and Wical (1999)*** evaluated attentional difficulties in children with complex partial seizures, 12 children with complex partial seizures with attention deficient hyperactivity disorder; 21 children with

CPS without ADHD; 22 children with ADHD; and 15 control children. Each child completed a computerized performance test, which evaluated sustained attention, inhibition of response, response time, and consistency of response. The results found poorest performance on the computerized performance test by the complex partial seizures with attention deficient hyperactivity disorder group. Particular difficulty in attention was found for children with epilepsy regardless of the ADHD diagnosis. These findings suggested that epilepsy may predispose children to attention problems that can significantly interfere with learning.

***Dunn et al. (2003)*** assessed 175 epileptic children age range 9 to 14 years for evidence of ADHD. The primary caregiver completed both the Child Behavior Checklist (CBCL) and the Child Symptom Inventory (CSI) or Adolescent Symptom Inventory (ASI). They found that (38%) of the children had a diagnosis of ADHD. In addition, they found that sex, seizure type, and focus of seizure discharge were not predictors of symptoms of ADHD. Neither seizure type nor localization of seizure focus have consistently predicted ADHD, while the seizure frequency was significantly associated with diagnosis of ADHD.

In agreement with our findings of having ADHD diagnosis more in patients with generalized seizures (18.03%) than in those with focal seizures (11.86%), in ***Dunn et al. (2003)*** sample, more children with generalized seizures had a symptoms of ADHD compared with

children with partial or absence seizures. This is similar to the finding of ***Hempel et al. (1995)*** who noted that children with intractable generalized seizures were more likely to meet diagnostic criteria for ADHD.

***Mood & Anxiety disorders:***

In our study, we found 19.15% of the sample having mood and anxiety disorders, as we had depression in 3.33% (n=4), hypomania in 0.83% (n=1), social anxiety disorder in 5.83% (n=7), specific phobias in 3.33% (n=4), generalized anxiety disorder in 1.67% (n=2), separation anxiety in 0.83% (n=1), while adjustment disorder was in 0.83% (n=1). Depression was co-morbid with generalized anxiety disorder in 1.67% (n=2), and with social anxiety disorder in 0.83% (n=1).

These rates are lower than most of other studies. It can be explained by considering that childhood mood and anxiety disorders can be particularly difficult to recognize. Given the internalizing nature of symptoms, caregivers who are mostly illiterate or not well educated in our sample, are often unaware of depressed mood or anxiety symptoms in their children. Children do not necessarily show sadness or inability to enjoy things but may be irritable, oppositional, and aggressive.

In ***Saadani et al. (2002)*** study, 20 children with newly diagnosed idiopathic generalized tonic clonic seizures, who had never received antiepileptic drugs, were examined for mood disorders using Child Depression Inventory (CDI), after being diagnosed according to DSM-

IV criteria. They found 30% (n=6) of the cases to have mood disorders, either major depression, dysthymia, or adjustment disorder depressive type.

***Said et al. (2002)*** designed a study to assess rates of anxiety symptoms among pediatric patients with idiopathic generalized epilepsy. They administered children anxiety scale (CAS) to 23 patients aged 10-18 years and 23 healthy controls subjects. They found that (73%) of the patients were fulfilling the criteria of generalized anxiety disorder. The onset of this disorder in (13%) of cases preceded the onset of epilepsy.

Their rates were higher than ours *(Table 10 & Figure 9)*, this can be explained by methodological differences either in sample size, selection of cases, or tools used for assessment of patients.

Studies vary in their findings regarding variables associated with depression and anxiety in youth with epilepsy. Some found an association with seizure variables, such as seizure control, AED polytherapy, age of onset, duration of illness, and the type of epilepsy ***(Oğuz et al., 2002;Baki et al., 2004; Caplan et al., 2005; Sabbagh et al., 2006)***, but others do not ***(Dunn et al., 1999; Davis et al., 2003).***

In ***Dunn et al. (1999)*** cross-sectional study, data were collected on 115 adolescents aged 12 to 16 years who had epilepsy. Demographic (age, gender), seizure (severity, age of onset), family (stress, resources, relationships), mother

(perceptions of stigma, depression), and child (attitude toward epilepsy, satisfaction with family relationships, coping, perceptions of control) variables were assessed by questionnaire and standardized scales. Depression was measured by the Children & adolescent's Depression inventory and the Anxiety/Depression subscale of the Youth Self-Report. In this sample, (23%) of subjects had symptoms of depression. Significant predictors of depression as measured by the Children & adolescents Depression Inventory were youth & adolescents attitude toward epilepsy, youth satisfaction with family relationships, and unknown locus of control or external locus of control for socially powerful others.

***Oğuz et al. (2002)*** evaluated the anxiety and depression in epileptic children to compare their results with that of a healthy control group and to determine the relationship of anxiety and depression scores to epilepsy-related factors. The State Trait Anxiety Inventory (STAI) and Children's Depression Inventory (CDI) were applied to 35 patients with epilepsy aged 9 to 18 years and to 35 healthy children who served as the control group. Both study and control groups were divided into two age groups. The mean state anxiety score, trait anxiety score, and depression scores were significantly higher in the 12- to 18-year age group of epileptic children than in the control group. Among the epilepsy-related factors, whereas epilepsy duration, seizure frequency, and polytherapy were determined to increase anxiety and depression, age of seizure onset, seizure type, and

electroencephalographic findings were not related to anxiety and depression.

***Baki et al. (2004)*** studied 35 children and adolescents with seizures, 35 gender-matched healthy controls, administered the Kovacs Child Depression Inventory (CDI) and State–Trait Anxiety Inventory for Children (STAI) to the children. Patients with epilepsy had higher CDI scores, whereas the STAI scores did not differ between cases and controls. Among the epilepsy-related factors, seizure type, age at seizure onset, seizure frequency, and longer duration of epilepsy were not associated with depression in this study group of children with epilepsy.

The number of studies that have examined anxiety in children with epilepsy is small, and the prevalence remains unknown ***(Baki et al., 2004).*** Our findings revealed more severe anxiety in patients with focal seizures than the patients with generalized seizures *(Table 28 & Figure 21).* This may be explained by considering that temporal lobe epilepsy which is the most common focal type, in which epileptogenic lesions are able to disrupt limbic connections ***(Engel et al., 2002).*** Recent literature linking these structures, the amygdala in particular, to generalized anxiety disorder ***(Chau et al. 1999)*** and subjective anxiety in social phobia ***(Tillfors et al., 2001).***

The amygdala may provide the affective tone to perceptions and experiences. Studies demonstrate a role of the amygdala in verbal and nonverbal recognition of emotions ***(Furmark et al., 1997)***, as well as fear-induced

anxiety ***(Davidson et al., 1999)*** and in provoked anxiety ***(Malizia, 1999).*** The projections of the central nucleus of the amygdala to the locus coeruleus and hypothalamus have been found to be responsible for the arousal and autonomic responses associated with fear and anxiety ***(Pellock, 2004).***

## Cognitive impairment among epileptic children and adolescents:

Regarding cognitive impairment we were concerned by two domains:

1. Discrepancy between verbal and performance IQ, which denotes cognitive decline.
2. Impairment in visual perception, memory, and visuo-constructive abilities.

Our findings revealed that 25% (n=30) having discrepancy between verbal and performance IQ, while examination of visual perception, memory, and visuo-constructive abilities revealed impairment in 48.17% (n=59) of the studied sample *(Table (11, 12) & Figure (10,11)).*

This is consistent with the epidemiological studies which report that cognitive functions (attention, reaction time, spatial and emotional memory, and specific learning disorders, such as those affecting reading, writing, or mathematical skills) are more frequently impaired in people with epileptic seizures than in the general population, even in children with normal intelligence ***(Cornaggia et al., 2006).***

To date, a very small number of studies have examined cognition in children with epilepsy ***(Bourgeois et al., 1983; Stores et al., 1992; Williams et al., 1998; Kolk et al., 2001; Oostrom et al., 2003).*** Three of the five studies identified cognitive impairments at epilepsy onset, and mixed results may be attributable, at least in part, to the variable age ranges, test batteries and epilepsy characteristics across studies. Especially interesting are reports of academic underachievement before and/or at the onset of idiopathic epilepsy ***(Oostrom et al., 2003; Berg et al., 2004; McNelis et al., 2005)***.

***Bourgeois et al. (1983)*** performed a prospective study that tested the stability of the IQ in children with seizure disorders. Seventy-two children with epilepsy underwent psychological evaluations within two weeks of initial diagnosis and yearly thereafter for an average of 4 years. The mean IQ for all the children with epilepsy was 99.7 ± 20.2, at the time of the initial test. This score did not change appreciably with time. Eight of the 72 epileptic patients (11.1%), however, had a persistent decrease in IQ of 10 points or more. These patients had a higher incidence of drug levels in the toxic range, their epilepsy was more difficult to control, and their seizures began at an earlier age. Data analysis revealed that the number of drugs to which the patient became toxic and the age at seizure onset were the two best predictors of ultimate IQ. Total number of seizures and seizure control were less good predictors, according to this method of analysis. The findings suggest that, in younger children in particular, total seizure control

should not be achieved at the price of repeated episodes of drug toxicity. These findings are similar to ours *(Table 22)* regarding the mean TIQ among patients with generalized seizures (89.475 ± 9.4), and the mean TIQ among patients with focal seizures (93.525 ± 11.836), yet we did not examined the effect of seizure related variables on TIQ.

In ***Stores et al. (1992)*** study, Information from standardized tests of intelligence, school attainments, attention, memory and visuo-motor function, together with parent and teacher questionnaire information about various aspects of behavior, was obtained for 63 schoolchildren with newly diagnosed epilepsy before treatment with sodium valproate or carbamazepine, and again at intervals for a total period of 12 months. The same information were collected on 47 matched controls. The result showed that both drugs were effective in most cases at modest dosage without causing notable psychological effects 12 months into treatment. Modest and temporary adverse cognitive effects seen earlier in treatment could have been the result of uncontrolled seizure discharge. Some psychological abnormalities in the children with epilepsy were evident before treatment suggesting early unwanted effects of the epileptic process itself.

***El-Gamal et al. (1996)*** applied Luria-Nebraska Neuropsychological battery for children on 66 epileptic patients and 23 control subjects. Interestingly, although, significant difference was not reached when children with TLE were compared to controls, however many functions appear to be more affected in patients. Among these

functions are motor, writing, reading, arithmetic, and memory functions.

Also, they have found impairment in the subscale that measures visuo-perceptual abilities by drawing and copying geometrical figures. The visuo-perceptual disturbances became evident with increasing complexity of the task. Their findings are consistent with our finding that (49.17%) of our patients had impairment in their visual perception, visual memory, and visuo-constructive abilities.

***Kolk et al. (2001)*** performed neuropsychological examination on 44 children aged from 4 to 9 years. The children were divided into three groups: 18 children suffering from congenital hemiparesis with chronic partial epilepsy, 12 children with newly diagnosed partial epilepsy prior to anti-epileptic treatment, and 14 healthy controls. Children with congenital hemiparesis and epilepsy had a more clearly expressed cognitive dysfunction, than children with newly diagnosed partial epilepsy. The profile of cognitive weakness appears to be diffuse and quite similar in both groups, and it did not demonstrate a clear effect of lateralization, according to the side of epileptic electroencephalogram discharges. Children within both groups are likely to have a high risk of developing attention, phonological, visuo-perceptual, and memory deficits in their life. Especially interesting and surprising was the fact that the newly diagnosed epilepsy group demonstrated impairment not only in attention, visuo-perceptual and short-term memory skills, but also in

auditory perception, lexical function, and the comprehension of speech.

***McNelis et al. (2005)*** performed a study to identify variables associated with academic achievement in children at 12 months after a first-recognized seizure. Duration of illness, and age of onset of seizures were not included in the study. The illness characteristic used was seizure severity, a large component of severity was frequency. They found that seizure severity was strongly associated with teacher ratings of academic under-achievement.

***Hermann et al. (2006)*** study characterized neuropsychological status, brain structure and their interrelationship in children with recent-onset epilepsy compared with healthy controls. Children (age: 8–18 years) with recent onset idiopathic epilepsy (n = 53) and healthy controls (n=50) underwent comprehensive neuro-psychological assessment and quantitative volumetric measurement of segmented (grey and white matter) volumes of total cerebrum and lobar regions. Compared with controls, children with recent-onset epilepsy exhibit a pattern of mild diffuse cognitive impairment, regardless of epilepsy syndrome, as well as academic underachievement that in a subset of children preceded the first recognized seizure. Controls show a strong association between cognitive development and increasing cerebral tissue volume (especially white matter volume), an association that is absent in children with epilepsy. Children with a history of academic achievement problems exhibit the

most abnormal cognitive function and have significant volumetric reductions in left occipital and parietal lobe grey matter. Patients with idiopathic epilepsy exhibit cognitive dysfunction and academic underachievement at the onset of the disorder, irrespective of epilepsy syndrome, and indications of antecedent neuro-cognitive impairment are present in a subset of children. These findings suggest an antecedent neurobiological abnormality of uncertain etiology.

Similarly, the results of tests in children with newly diagnosed epilepsy who had not started antiepileptic medications showed significantly poorer performance in attention, reaction time, and visual memory, with a trend for academic underachievement ***(Oostrom et al., 2003).***

Cognitive and behavioral changes in epilepsy have a multi-factorial etiology, which includes the epilepsy itself, treatment of epilepsy (antiepileptic drugs (AEDs) or surgery), reactions to epilepsy (stigma, social marginalization, and familial dynamics), and any associated brain dysfunction and/or damage ***(Cornaggia et al., 2006).***

***The epilepsy itself:***

Our results revealed that duration of epilepsy is considered as a risk factor for impairment in visual perception, memory, and visuo-constructive abilities *(Table 16).* This is in agreement with ***Schoenfeld et al. (1999)***, as they reported that the duration of epilepsy is related to

cognitive problems more than emotional and behavioral problems. In contrast, ***El-Gamal et al. (1996)*** found no relation between duration of illness and Luria-Nebraska neuropsychological battery scales' results.

This can be explained by knowing the fact that epileptogenicity causes enduring changes of brain function and structure in many different ways, which can result in cognitive and behavioral alteration ***(Holmes, 2005).*** In infancy or in early childhood, abnormal recurrent synaptic bombardment of distant projection areas, caused by repeated ictal and interictal epileptiform discharges, can adversely affect the development of normal neuronal integration. In the mature brain, this abnormal synaptic activity may induce plastic changes through kindling mechanisms, and impair the naturally occurring homeostatic seizure-suppressing mechanisms which maintain the interictal state, with adverse consequences on the normal neuronal function ***(Engel et al., 2002).*** There is evidence that single complex partial and secondarily generalized seizures may be associated with neural damage ***(Rabinowicz, et al., 1996)***, and that brain extracellular glutamate may build up in partial seizures to neurotoxic levels ***(During and Spencer, 1993)***, which can be predictors of behavioral problems. Moreover, epileptic seizures are known to disrupt sleep patterns and endocrine functions, which can result in an alteration of cognition and behavior ***(Lambert, 2001).***

***Treatment of epilepsy:***

Our results confirm that polytherapy have negative impact on the cognitive abilities, as we found that patients who had been prescribed polytherapy had more impairment in visual perception, memory and visuo-constructive abilities than those on monotherapy *(Table 25 & Figure 19).*

In ***Nasr et al. (1993)*** study, it was found that patients under polytherapy performed poorly on most scales of Luria-Nebraska Neuropsychological battery for children, compared to patients under monotherapy.

Reviewing literature revealed that cognitive functions, including psychomotor speed, vigilance, memory, attention, and memory, are affected by AEDs in different ways; children are especially vulnerable to cognitive adverse effects ***(Cornaggia et al., 2006).***

AEDs exert dosage-dependent effects on cognitive functioning, which can be exacerbated by AED polytherapy. The magnitude of AED-related cognitive dysfunction is generally modest in monotherapy and when the AED is present at therapeutic serum concentrations ***(Park and Kwon, 2008).***

Cognitive inefficiencies are a common adverse effect of many medications, including AEDs and psychotropic drugs. Such agents can markedly interfere with attention and encoding aspects of memory; some agents, such as

phenytoin (used long-term), produce structural damage, causing insidious and irreversible cognitive impairment ***(Bortz, 2003).***

During the past decade, only a few controlled trials have systematically examined the behavioral and cognitive side effects of AEDs in epileptic children. Data are available mostly from case reports, cross-sectional studies in adults, mixed age populations, or healthy volunteers. Therefore, available data regarding the specific causal effects of AEDs on the cognitive and behavioral problems in intellectually normal children with epilepsy are either insufficient or inconclusive ***(Plioplys et al., 2007).***

Higher rates of attention problems have been previously reported in children with epilepsy. On comparing patients with generalized seizures with those of focal seizures in our sample *(Table 26 & Table 29)*, we found that there was significant difference between them in:

1. TIQ
2. Attention problems

Indicating more impairment in the generalized seizure group which is consistent with some previous researches.

Also, ***Abdulghani et al. (1994)*** in their study of value of EEG in prediction of behavioral changes in epileptic children, found that patients with generalized seizures had worse IQ scores than patients with focal fits.

Cognition might also be affected when examined directly in childhood. When studying intelligence in 162

children with diverse epilepsy syndromes who presented to a tertiary care centre for EEG video monitoring, ***Nolan et al. (2003)*** reported that intellectual ability fell below the normed mean for age across diverse epilepsy syndromes, even after taking into account covariates such as age of onset, seizure frequency, and number of medications. However, this result does not apply to performance across specific cognitive domains ***(Hermann et al., 2008).***

***Aarts et al. (1984)*** found that generalized epilepsies are more likely to produce impairment of attention than focal epilepsies. Many studies have shown transient cognitive impairment (TCI) in association with subtle impairment of attention during subclinical epileptiform discharges. Tests of attention and recall show TCI during one third of discharges and in two-thirds of patients with absence epilepsy ***(Binnie et al., 1991; Goyal, 2007).***

Cognitive impairment can be prevented by treating epilepsy early and effectively. Children with specific learning difficulties and memory problems can benefit greatly from appropriate management. There are many causes of behavioral disturbance in children with epilepsy. These causes include the epilepsy itself, treatment of the epilepsy, reactions to the epilepsy, associated brain damage/dysfunction and causes that are equally applicable to children who do not have epilepsy. Identifying the cause or causes in each child allows rational management to be provided. Antiepileptic treatment with medication or surgery can either improve the situation or make matters worse. The treatment should be tailored to

the needs of the individual child. Skilled management of children with epilepsy who have cognitive impairment and/or behavioral problems can be very rewarding both for the family and for the professionals involved ***(Besag, 2002).***

## Effects of seizure related factors on behavioral and cognitive problems in epileptic children and adolescents:

The debate still continues regarding the possible role of epilepsy related variables in the psychopathology of cognitively normal children with idiopathic epilepsy ***(Plioplys et al., 2007).*** The majority of studies have found no association among age at seizure onset, seizure frequency, seizure type, lateralization of seizure focus, and psychopathology in children with epilepsy ***(Austin et al., 1996; Caplan et al., 2004)***, albeit new findings on a large sample of children with childhood absence epilepsy and average intelligence imply a role for seizure variables ***(Siddarth et al., 2006).***

Our study was concerned by studying the relation between seizure related factors (age of onset, duration of epilepsy *(Table 14, 15, 16 & Figure 13)*, frequency *(Table 17, 18, 19 & Figure 14, 15, 16)*, duration of epilepsy without receiving treatment *(Table 20, 21, 22)*, and pattern of drug therapy *(Table 23, 24, 25 & Figure 17, 18, 19 )*) on one hand, and behavioral and cognitive problems on the other hand.

We found significant relation between the frequency of seizures and prolonged duration of epilepsy without receiving treatment, and psychiatric co-morbidity. While there was significant relation between duration of epilepsy and receiving polytherapy, and having impaired visual perception, memory, and visuo-constructive abilities.

***El-Gamal et al. (1996)***, regarding cognitive functions, they found no significant correlation between age of onset of seizures, duration of illness, frequency of fits, or pattern of drug therapy and neuropsychological scales' results.

***Schoenfeld et al. (1999)*** found that earlier age at onset of recurrent seizures was associated with poorer performance across all cognitive domains, except for motor skills. This is inconsistent with our findings as we had no positive correlation between age of onset of epilepsy and cognitive impairment in our sample *(Table 15 & 16).*

They also found that frequency of seizures (either complex partial or secondarily generalized) during the past year was not significantly related to cognitive functioning. Moreover, cognitive performance was not significantly associated with laterality of epileptiform EEG abnormality across the cognitive domains. In their study, there was a pattern of poorer performance by those on polypharmacy compared with monotherapy. This is in agreement with our findings that the patients on polytherapy had more impairment in visual perception, visual memory, and visuo-constructive abilities *(Table 25 & Figure 19).*

In agreement with our findings that the frequency of seizures is a significant correlate and predictor of psychiatric co-morbidity *(Table 17 & Figure 14)*, ***Schoenfeld et al. (1999)*** found that the frequency of seizures was the strongest and most consistent correlate of social competence and behavioral problems; increased frequency of CPS was significantly associated with 10 out of 14 CBCL scales and frequency of secondarily generalized seizures was associated with five CBCL scales. These findings are consistent with other reports ***(Hoare and Kerley 1991, Austin et al. 1992).***

In contrast, age at onset of recurrent seizures was clearly less strongly associated with behavioral adjustment in ***Schoenfeld et al. (1999)*** study. Additional analyses failed to detect a significant relationship between CBCL scale scores and laterality of epileptiform EEG focus, duration of active epilepsy, history of status epilepticus, or monotherapy/ polytherapy AED regimen. These findings agree with what we found in our study, that there was no significant correlation between age of onset of epilepsy, its duration, pattern of drug therapy, and psychiatric co-morbidity.

***Austin et al. (1992)*** studied 136 children aged 8-12 years with epilepsy receiving prescribed AEDs, with no other chronic conditions, who had an IQ of at least 70. The behavioral functioning of the child, was measured by the mothers' ratings on the Child Behavior Checklist (CBCL). No differences in behavior problems were noted between

those receiving one AED and those receiving two or more AEDs. Child behavior problems across the various epilepsy syndromes was not statistically significant. A contrast between children with primary syndromes and those with secondary syndromes was also non significant. Increased seizure frequency was associated with more behavioral problems.

***Austin et al. (2000)*** conducted a 4-year follow-up study of behavior problems in children with either epilepsy (n = 115) or asthma (n = 105) to identify changes in behavior Problems**.** All children were between ages 8 and 13 years and had been diagnosed with their respective conditions for ≥ 1 year at entry into the study. Behavior problems were measured by using the mother's rating on the Child Behavior Checklist. Baseline and follow-up behavior problem scores were examined to see if significant changes occurred over the observation period of the study. Within the epilepsy sample, there was a significant increase in total behavior problems, internalizing problems, and externalizing problems. They found that behavior and cognitive problems increased with high seizure severity at both baseline and follow-up became substantially worse over the 4-year period, specifically in girls.

In ***Austin et al. (2002)*** study, their major finding was that seizure recurrence significantly predicted behavior problems. Possible explanations for this relation are that (a) seizures and behavior problems are associated because both are related to an underlying factor, (b) seizure activity

per se disrupts behavior, or (c) children have a negative psychological response to seizures.

The underlying mechanism(s) for the association between seizure frequency in the past year and behavior problems remains to be clarified. Seizure frequency could impact behavior in the context of the nature and pattern of cerebral disturbance underlying the seizures ***(Schoenfeld et al. 1999).*** Seizure frequency may be an important risk factor because frequent non-convulsive seizures (i.e. absence seizures) were associated with attention deficits and slow information processing ***(Aldenkamp and Arends, 2004).*** Increased exposure to psychosocial factors such as parental distress about seizure activity, the stigma, social isolation, and family dysfunction may accompany increased seizure frequency, that may precipitate behavioral problems ***(Schoenfeld et al. 1999).***

In contrast, ***Caplan et al. (2004)*** found that seizures factors were unrelated to measures of psychopathology. The prolonged seizure, febrile convulsions and the seizure frequency, AEDs component were significantly related to cognitive impairment.

According to ***Freilinger et al. (2006)*** higher Child Behavior Checklist scores were associated with epilepsy-related factors as etiology, earlier age at onset, and polypharmacy. There were no statistically significant associations between the Child Behavior Checklist scores and seizure symptoms and frequency and EEG at the time of evaluation.

In contrast to our study that revealed significantly associated between behavioral problems and seizure frequency, while there was no association between behavioral problems and age of onset of epilepsy and its duration, ***Høie et al. (2006)*** studied psychosocial problems, cognitive function, and socioeconomic status in 117 children with epilepsy aged between 6 and 13 years and in randomly selected controls matched with 117 children for sex and age. Behavioral problems were assessed by (CBCL), while cognitive function was evaluated using Raven Matrices or WISC-R. They found that the early age at seizure onset was associated with more behavior problems. In addition, they found no association between seizure frequency and behavioral problems. This unexpected observation was in contrast to the significant relationship between behavioral problems and high seizure frequency reported in hospital-based studies.

Our findings that revealed no significant association between pattern of drug therapy and behavioral problems confirmed ***Høie et al. (2006)*** & ***Schoenfeld et al. (1999)*** findings. Also they found no significant relationship between antiepileptic drug treatment or EEG factors and behavior problems. Similarly, ***Bourgeois (1998)*** has found AEDs are not a major cause of cognitive or behavioral problems.

In contrast to our findings, in ***Hoare and Kerley (1991)*** study, early age at seizure onset was associated with more behavior problems, whereas our findings was in

agreement with ***Sabaz et al. (2001)*** study that found no significant relationship between CBCL problem scales and age at epilepsy onset, medications taken, while in contrast to our findings they found no significant association between CBCL problem scales and frequency of seizures.

To our knowledge there is no enough research work that is concerned with the relation between prolonged duration of epilepsy without receiving treatment and psychopathology in epileptic children and adolescents, to compare our work to it. Similarly, the relation between seizure related variables and the discrepancy between verbal and performance IQ, was not much researched in the reviewed literature.

# ***Summary***

The interest in studying the relation between epilepsy and psychiatric disorders in children reflects the persistent interest in studying the different presentations of brain pathology, and whether they are different entities or both are of common pathology yet differs in its clinical presentations.

Our study was designed to test the hypothesis that children and adolescents with epilepsy have increased rates of co-morbid psychiatric disorders than healthy children. These psychiatric problems are not well revealed, at least in the Egyptian patients.

The aim of the study was to detect the rate of psychiatric co-morbidities in the epileptic children and adolescents, and correlating them with different seizure related variables.

A sample of one hundred and twenty eight patients were selected from either new or follow up cases, who were attending the outpatient clinics, neuropsychiatry department, Ain Shams University Hospitals. Eight cases were excluded because of low IQ.

Patients evaluated in this work involved 120 (61 patient with generalized seizures, and 59 patient with focal seizures) epileptic children and adolescents who were assessed with Wechsler Intelligence Scale for Children (WISC), The Benton Revised Visual Retention Test (BVRT), Mini International Neuropsychiatric Interview (MINI), Child Depression Inventory (CDI), Revised Children's Manifest Anxiety Scale (RCMAS), and Revised Behavior Problem Checklist (RBPC).

Patients in this study were not only compared to the control group constituted of 30 healthy children and adolescents, but also compared among themselves regarding IQ, and the severity of the psychiatric illnesses.

All data gathered were recorded, tabulated and transferred on Statistical Package for Social Science (SPSS) version 16. Many statistical methods were used for analysis of data.

Our study resulted in the following:

- Demographic variables: 55% of the sample were males, while 45% were females, with age mean ± SD = 12.317 ± 2.177.

- Only 22.69% of the sample had positive family history of epilepsy, while 77.31% had no family history of

epilepsy. On the other hand, only 5.04% of the sample had positive family history of psychiatric illness, while 94.96% hadn't.

- Febrile convulsions was found only in 7.56% of the studied sample.

- Psychiatric co-morbidity was found in 48.33% of the patients, most of them were suffering of focal seizures. They were distributed as follows:
  - ***ADHD & Disruptive disorders****:* 15% of the sample were diagnosed as ADHD, 5% as conduct disorder, and 0.83% as oppositional defiant disorder.

  - ***Mood and anxiety disorders****:* 3.33% of the sample were diagnosed as depression, while among anxiety disorders social anxiety disorder was the most prevailing diagnosis with 5.83%, followed by specific phobias with 3.33%, generalized anxiety disorder with 1.67%, while separation anxiety disorder and adjustment disorder each with 0.83%.

  - ***Co-morbidities*** was mostly between ADHD and conduct disorder with 5.83%, followed by ADHD and specific phobia in 1.67%, while depression was co-morbid with generalized anxiety disorder in

1.67% and it was co-morbid with social anxiety disorder in 0.83%.

- On examining the cognitive functions of the patients we found 25% of the sample having discrepancy between verbal and performance IQ, and 49.17% of the sample had impaired visual perception, memory and visuo-constructive abilities.

- By studying seizure related variables in relation to psychiatric co-morbidity and cognitive impairment we found significant correlation between frequency of seizures and prolonged duration of epilepsy without receiving treatment, and psychiatric co-morbidity, while there was significant correlation between duration of illness and receiving polytherapy, and having impaired visual perception, memory and visuo-constructive abilities.

- On comparing the children suffering of generalized seizures with those who suffer of focal seizures we found significant difference in TIQ and attention which were more worse in the generalized group, while those of the focal group revealed more severe anxiety and motor excess problem than those of the generalized group.

- On evaluating predictive factors we found that frequency of seizures and prolonged duration of illness without receiving treatment were the significant correlates among seizure related variables while type of seizure, age of onset and duration of epilepsy were non significant.

## ***Recommendations***

Although there paucity of studies specially aiming to define behavioral disturbance in epileptic children, three is indeed empirical evidence showing that children with epilepsy exhibit more psychopathology than children from the general population. Factors common to chronic illness that are medication regimen, frequent hospitalization, disruption of family life, and limitation of activities, rather than epilepsy itself may impede normal developmental processes in epileptic children, and could have negative social and psychological consequences for both the child and the family.

### ***Research recommendations:***

- Future research on psychopathology in children with epilepsy should focus on a multi-factorial framework, considering both neurological and psychosocial factors (including family processes) that may contribute to psychopathology.

- An integrated model explaining interaction between all implicated factors is largely needed. For this purpose, more longitudinal follow up studies are needed and samples must be more representative.

- New studies are needed to expand our understanding to the role of seizure related variables, underlying brain dysfunction, genetic factors, and social/environmental factors in the pathophysiology of cognitive and psychiatric disturbances in epilepsy.

- Future studies that collect behavior ratings from other sources (e.g. teachers) would be useful in distinguishing between the possible mechanisms for the relation between seizure activity and behavioral problems.

- There is need for evidence based data that show the effectiveness of interventions for the cognitive, psychiatric and social comorbidities of epilepsy in children and adolescents.

- More research is needed for designing and evaluating preventive and therapeutic approaches, identifying groups at risk for social and psychological problems and those factors predicting lack of adherence to treatment.

## ***Clinical recommendations:***

- Clinicians should be aware that children with epilepsy are at increased risk for the development of cognitive and behavioral problems. Moreover, they should take

into account that some problems may be common to children with a chronic disease, whereas other problems tend to be relatively specific to epilepsy. This may have implications for treatment.

- Neuropsychological assessment may be particularly useful for documenting cognitive status and for identifying potentially reversible causes of functional impairment herald by psychiatric sequelea.

- Evaluating cognitive functions prior to adding or switching an AED.

- If certain AED impairs cognition, trying another AED with differing pharmacologic profile might be successful. Slow titration to the lowest effective dosage and avoiding polytherapy and overmedication is a critical key in managing epileptic children.

- Psychiatric illness should be thoroughly addressed, as the optimal outcome depends on the coordinated multi-disciplinary management strategies aiming for beyond mere seizure control.

- As a final point, clinicians should incorporate family factors in their diagnosis and treatment of psychopathology in children with epilepsy.

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# الملخص العربي

**إنَّ الإهتمام بدراسة العلاقة بين مرض الصرع و الاضطرابات النفسية لدى الأطفال و المراهقين، يعكس الإهتمام المستمر بدراسة الأشكال الإكلينيكية المختلفة لاعتلال الدماغ، و ما إذا كان كلاهما يعبر عن مرض بذاته، أو أن لكلاهما اعتلال واحد و لكنه يعبر عن نفسه بأعراض مختلفة.**

**صممت دراستنا لاختبار الفرضية القائلة بأن الأطفال والمراهقين المصابين بالصرع تزداد معدلات الاضطرابات النفسية عندهم أكثر من الأطفال الأصحاء. و هذه المشاكل النفسية لا تكتشف جيدا، على الأقل في المرضى المصريين.**

**والهدف من الدراسة هو الكشف عن معدل الاضطرابات النفسية المصاحبة لمرض الصرع عند الأطفال و المراهقين، و المحاولة لإيجاد علاقة بين حدوثها و المتغيرات الخاصة بمرض الصرع.**

**تم إختيار عينة من مائة وثمانية و عشرين مريضا من المترددين على العيادات الخارجية بقسم الأمراض النفسية و العصبية بمستشفيات جامعة عين شمس، إما من الحالات الجديدة أو من المتابعات و قد تم إستبعاد ثماني حالات بسبب انخفاض معدل الذكاء عن المطلوب للدراسة.**

**تم تقييم مئة و عشرين طفل و مراهق من مرضى الصرع بهذا العمل وذلك عن طريق:**

- **اختبار ذكاء باستخدام مقياس ويكسلر للأطفال**

- **اختبار بينتون للارتجاع البصري**
- **المقياس العالمي المصغر النفسي العصبي للأطفال (ميني كيد)**
- **استبار الاكتئاب للأطفال**
- **مقياس القلق للأطفال**
- **اختبار السلوك للأطفال**
- **مقياس شالفونت لشدة النوبات الصرعية**
- **نتيجة لحساب توقيت النوبات**
- **رسم المخ**
- **أشعة مقطعية أو أشعة رنين مغناطيسي على المخ لبعض الحالات**

**تمت مقارنة مجموعة الدراسة بالمجموعة الضابطة و التي تكونت من ثلاثين طفلا و مراهقا بالإضافة إلى مقارنتها فيما بينها بشأن معدلات الذكاء و شدة الاضطرابات النفسية.**

**كل البيانات المجمعة تم تسجيلها, و جدولتها و نقلها على البرنامج الإحصائي للعلوم الإجتماعية الإصدار رقم 16 وتم استخدام العديد من المعادلات الإحصائية لتحليل البيانات.**
**و أسفرت الدراسة عن النتائج الأتي ذكرها:**

- **المتغيرات الديمغرافية : 55 ٪ من العينة كانوا من الذكور ، في حين أن 45 ٪ كانوا من الإناث ،و كان متوسط السن في العينة = 12.317 ± 2.177 سنة.**

- **فقط 22.69 ٪ من العينة كانت إيجابية للتاريخ العائلي لمرض الصرع ، في حين أن 77.31 ٪ لم يكون تاريخ عائلي للصرع. من ناحية أخرى ، لم يكن هناك سوى 5.04 ٪ من العينة إيجابية للتاريخ العائلي للمرض النفسي ، بينما 94.96 ٪ كانت النتيجة سلبية.**

- **التشنجات الحرارية كانت متواجدة فقط في 7.56 ٪ من العينة التي شملتها الدراسة.**

- **وجدنا أن 48.33 ٪ من المرض يعانون من اضطرابات نفسية ومعظمهم كانوا يعانون من نوبات بؤرية, كانت موزعة على النحو التالي:**
  - **اضطراب فرط الحركة و قلة الإنتباه و اضطرابات المسلك:**
    **15٪ من العينة تم تشخيصها على إنها اضطراب فرط الحركة و قلة الإنتباه, 5٪ اضطراب الجناح, و 0.83 ٪ اضطراب العناد الشارد.**

  - **اضطرابات القلق والاضطرابات المزاجية:**
    **3.33 ٪ من العينة تم تشخيصها بالإكتئاب ,في حين أن من بين اضطرابات القلق كان اضطراب القلق الإجتماعي هو التشخيص الأكثر شيوعا بنسبة 5.83 ٪, يليه اضطراب الرهاب الخاص بنسبة 3.33 ٪, اضطراب القلق العام بنسبة 1.67 ٪, في حين أن اضطراب قلق الإنفصال واضطراب التكيف كان بنسبة 0.83 ٪ لكل منهما.**

  - **وجود اكثر من اضطراب:**

**كانت معظمها بين اضطراب فرط الحركة و قلة الإنتباه و اضطراب الجناح بنسبة 5.83٪, تليها اضطراب فرط الحركة و قلة الإنتباه و الرهاب الخاص بنسبة 1.67 ٪, في حين كان الإكتئاب مع اضطراب القلق العام بنسبة 1.67 ٪ وكان مع اضطراب القلق الإجتماعي في 0.83 ٪.**

- **بدراسة الوظائف المعرفية للمرضى وجدنا في 25٪ من العينة تباين بين معدل الذكاء اللفظي والذكاء الأدائي, و 49.17 ٪ من العينة تعاني من ضعف الإدراك البصري ,الذاكرة البصرية و القدرات البصرية البنائية.**

- **من خلال دراسة المتغيرات الخاصة بمرض الصرع وعلاقتها بالمرضية النفسية وضعف القدرات المعرفية وجدنا ارتباط كبير بين كثرة عدد النوبات الصرعية وتأخير علاج الصرع, والمرضية النفسية ,في حين كان هناك ارتباط كبير بين مدة المرض وتلقي أكثر من دواء لعلاج الصرع و ضعف الإدراك البصري ,الذاكرة البصرية و القدرات البصرية البنائية.**

- **بمقارنة الأطفال الذين يعانون من نوبات عامه مع أولئك الذين يعانون من نوبة بؤرية وجدنا فارقا كبيرا في نسبة الذكاء والإنتباه والتي كانت أسوء في مجموعة النوبات العامة, في حين انمجموعة النوبات البؤرية كانت تعاني أعراض قلق وفرط حركه أشد.**

- **بتقييم العوامل التنبؤية وجدنا ان اهم العوامل التي تنبئ بحدوث اضطرابات نفسية كانتا كثرة عدد النوبات الصرعية وتأخر العلاج.**

## التوصيات :

على الرغم من أن هناك ندرة فى الدراسات التى تهدف خصيصا لتحديد الاضطرابات السلوكية فى الأطفال مرضى الصرع ، هناك فى الواقع الأدلة التجريبية التى تبين أن الأطفال الذين يعانون من الصرع أكثر عرضة للأمراض النفسية من الأطفال الأصحاء العوامل المشتركة بين الأمراض المزمنة التى هى نظام الدواء والعلاج فى المستشفيات بشكل متكرر ، واختلال الحياة العائلية ، والحد من الانشطة ، إضافة إلى نوبات الصرع نفسها قد تعوق العمليات العادية فى النمو لدى الأطفال مرضى الصرع ، ويمكن أن تكون لها عواقب إجتماعية ونفسية سلبية على كل من الطفل وعائلة 0

## توصيات بحثية :

• البحوث المستقبلية على الأمراض النفسية عند الأطفال المصابين بالصرع ينبغى أن تركز على وضع إطار متعدد العوامل ، معتبرا على حد سواء العوامل العصبية والعوامل النفسية والاجتماعية التى قد تسهم فى تكوين المرض النفسى 0

• نحتاج بشكل كبير إلى نموذج متكامل يوضح التفاعل بين جميع العناصر المسببة للاضطرابات النفسية 0 لهذا الغرض ، نحتاج إلى دراسات طولية تتبعية , والعينات يجب أن تكون أكثر تمثيلا 0

•هناك حاجة إلى دراسات جديدة لتوسيع فهمنا لدور المتغيرات ذات الصلة بالصرع ، اختلال وظائف المخ ، العوامل الوراثية ، والاجتماعية

**والبيئية فى الفيزيولوجيا المرضية للاضطرابات النفسية والمعرفية فى الصرع 0**

**• الدراسات المستقبلية التى تجمع المعلومات من مصادر أخرى ( مثل المدرسين ) ستكون مفيدة فى التمييز بين الأليات الممكنة للعلاقة بين نشاط النوبات الصرعية والمشكلات السلوكية 0**

**•هناك حاجة للبيانات التى تظهر فعالية التدخلات لحل المشاكل المعرفية والنفسية والاجتماعية المصاحبة لمرض الصرع لدى الأطفال والمراهقين 0**

**•المزيد من الأبحاث لازمة لتصميم وتقييم النهج الوقائي والعلاجى ، وتحديد الفئات المعرضة للخطر لمشاكل اجتماعية ونفسية ، وتحديد العوامل التى تتوقع عدم الامتثال للعلاج 0**

## توصيات سريرية :

**•الأطباء المعالجون ينبغى أن تدرك أن الأطفال الذين يعانون من الصرع معرضون بشكل متزايد للمشاكل المعرفية والسلوكية وعلاوة على ذلك ، ينبغى أن يأخذوا بعين الاعتبار أن بعض المشاكل قد تكون مشتركة 0 بين الأطفال الذين يعانون من مرض مزمن والأطفال مرضى الصرع ، فى حين أن مشاكل أخرى تميل إلى أن تكون محددة نسبيا لمرض الصرع 0 هذا قد يكون له تأثير على العلاج0**

**•التقييم العصبى النفسى قد يكون مفيدا بشكل خاص لتوثيق الحالة المعرفية ولتحديد أسباب الاضطراب الوظيفية التى تبشر بحلول تبعات نفسية 0**

**•تقييم الوظائف الإدراكية قبل إضافة أو تبديل الأدوية المضادة للصرع 0**

**•المعايرة البطيئة للأدوية المضادة للصرع إلى أدنى جرعة فعالة وتجنب تعدد الأدوية والجرعات الكبيرة , هو عامل رئيسي حاسم فى علاج الاطفال مرضى صرع 0**

**•ينبغى علاج المرض النفسي بشكل شامل ، حيث أن النتيجة المثلى تعتمد على استراتيجيات منسقة متعددة التخصصات تهدف لإدارة خارجة عن مجرد السيطرة على النوبات 0**

**• وكنقطة أخيرة ، ينبغى للأطباء إدراج العوامل العائلية فى تشخيص وعلاج الأمراض النفسية عند الأطفال المصابين بالصرع 0**

# أستبار الإكتئاب للأطفال

الأسم: السن:

التعليمات:
اقرأ العبارات التالية ثم اختار العبارة التي تصف مشاعرك و افكارك في الاسبوعين الاخريين:

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- ٠ بأبقى حزين أحيانا
  ١ بأبقى حزين في أوقات كثيرة
  ٢ بأبقى حزين طول الوقت

- ٢ مافيش حاجة حاتمشي كويس بالنسبة لي أبدًا
  ١ أنا مش متأكد من أن الأشياء و الظروف حتبقى كويسة بالنسبة لي
  ٠ الأشياء و الظروف حتبقى كويسة بالنسبة لي

- ٠ أنا بأعمل أغلب الحاجات بطريقة كويسة
  ١ أنا بأعمل حاجات كثيرة بطريقة غلط
  ٢ أنا بأعمل كل حاجة بطريقة غلط

- ٠ فيه حاجات كثيرة بتسليني
  ١ بعض الحاجات و الأشياء بتسليني
  ٢ مافيش حاجة بتسليني

- ٢ في كل الأوقات أنا وحش أو مش كويس
  ١ في أوقات كثيرة بأكون وحش أو مش كويس
  ٠ أحيانا بأكون وحش أو مش كويس

- ٠ أحيانا بأفكر في أشياء وحشة حاتحصل لي

# مقياس القلق للأطفال

**اعداد د. مايسة النيال  د. مدحت عبد الحميد (١٩٩١)**

الإسم:  السن:  الجنس:

المدرسة:  الصف الدراسي:

التعليمات:

العبارات اللي حتقراها دلوقت حاجات بتحصل لكتير زيك المطلوب منك إنك تشوف الحاجات دي بتحصل لك ام لا إذا كانت بتحصل لك ارسم دائرة حول كلمة نعم, و إذا كانت عمرها ما حصلت لك ارسم دائرة حول كلمة لا.

و لا تترك أي عبارة دون إجابة و شكرا.

| المظاهر الجسمية | المظاهر الفسيولوجية | المظاهر الحركية | المظاهر الانفعالية | المظاهر العقلية | المظاهر الاجتماعية | الدرجة الكلية |
|---|---|---|---|---|---|---|
| | | | | | | |

- ساعات كتير أحس بصداع في دماغي  نعم  لا
- بعرق كتير  نعم  لا
- حاسس إن نشاطي بقى غير الأول  نعم  لا
- أنا عصبي  نعم  لا
- دايما فكري مشغول ببكرة  نعم  لا
- احب اقعد لوحدي كتير  نعم  لا
- لما يكون بالي مشغول معرفش ابلع الكل أو ابلعه بصعوبة  نعم  لا
- وجهي يحمر بسرعة  نعم  لا

- مبقاش لي نفس ألعب مع أصحابي زي الأول نعم لا
- مش حاسس إني مرتاح نعم لا
- مش عارف اركز في دروسي نعم لا
- أنا ماليش أصحاب كتير نعم لا
- ساعات كتير ماما و بابا يقولوا لي وجهك أصفر نعم لا
- لما افكر في حاجة مهمة قلبي يدق بسرعة قوي نعم لا
- بقيت اتعب من أقل مجهود نعم لا
- حاسس إني زهقان نعم لا
- حاسس إن مستواي في المدرسة بقى أقل من الأول نعم لا
- أصحابي بيزعلوا مني علشان مبرضاش ألعب معاهم زي الأول نعم لا
- صحتي مش كويسة دلوقتي نعم لا
- ساعات بأحس إني مش عارف اتنفس و إني مخنوق نعم لا
- حركتي قلت عن الأول نعم لا
- ساعات باحلم أحلام وحشة بالليل نعم لا
- كل ما أفتح كتاب الاقي نفسي سرحت نعم لا
- خسرت أصحاب كتير في الايام الأخيرة نعم لا
- ساعات كتير ما بقاش لي نفس آكل نعم لا
- ساعات كتير بيجيني اسهال نعم لا
- ساعات يلاحظ علي الناس بعض الحركات العصبية نعم لا
- أنا دايما محتار نعم لا
- بقيت أنسى كل اللي اذاكره نعم لا
- ساعات بابقي مش عايز أشوف حد نعم لا
- وزني نقص في الأيام الأخيرة نعم لا
- ساعات أحس بزغللة في عيني نعم لا
- ساعات أحس إني مش قادر اقعد على كرسي لمدة طويلة و عايز اتحرك من مكان لمكان نعم لا
- أنا دايما مهموم نعم لا

- كل اللي يشوفني يقول لي إني كنت أحسن من كده في المذاكرة نعم لا
- بأحس إني متضايق من رأي الناس الأن نعم لا

| | |
|---|---|
| المظاهر الجسمية | ١-٧-١٣-١٩-٢٥-٣١ |
| المظاهر الفسيولوجية | ٢-٨-١٤-٢٠-٢٦-٣٢ |
| المظاهر الحركية | ٣-٩-١٥-٢١-٢٧-٣٣ |
| المظاهر الانفعالية | ٤-١٠-١٦-٢٢-٢٨-٣٤ |
| المظاهر العقلية | ٥-١١-١٧-٢٣-٢٩-٣٥ |
| المظاهر الاجتماعية | ٦-١٢-١٨-٢٤-٣٠-٢٦ |

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| ٤٦ | يتعاطى المخدرات مع أصدقائه | | | | |
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| ٧١ | أناني-لا يحب أن يشاركه أحد في شيء و طماع | | | | |
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| ٧٤ | لا يجدي معه مدح الكبار | | | | |
| ٧٥ | منعزل بسبب نشاطه العدواني-يكرهه الآخرون | | | | |
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| ٨٦ | متبلد العواطف- لا يحضن و لا يقبل أفراد أسرته | | | | |
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| ٨٩ | يشبه الببغاء في حديثه-يكرر ما يقال له | | | | |

١ أنا قلقان و مشغول من أن بعض الأشياء اللي مش كويسة حاتحصل لي
٢ أنا متأكد أن أشياء فظيعة حاتحصل لي

- ٢ أنا بأكره نفسي
١ أنا لا أحب نفسي
٠ أنا بأحب نفسي

- ٢ كل الحاجات الوحشة أو اللي مش كويسة بتكون بسببي أنا
١ كثير من الحاجات الوحشة أو اللي مش كويسة بتكون بسببي أنا
٠ مش دايما الحاجات الوحشة أو اللي مش كويسة بتكون بسببي أنا

- ٠ أنا ما بفكرش في أني أموت نفسي
١ أنا بأفكر أموت نفسي لكن مش حا أعمل كده
٢ أنا عايز أموت نفسي

- ٢ يوميا بأشعر أني عايز أعيط
١ في أوقات كثيرة بأشعر أني عايز أعيط
٠ أحيانا بأشعر أني عايز أعيط

- ٢ فيه أشياء بتضايقني طول الوقت
١ فيه أشياء بتضايقني أوقات كثيرة
٠ فيه أشياء بتضايقني أحيانا

- ٠ أنا بأحب أكون مع الناس
١ في أوقات كثيرة ما احبش أكون مع الناس
٢ أنا مش عايز أكون مع الناس أبدا

- ٢ أنا لا أستطيع أن أقرر أو أحدد رائي في الأشياء
١ من الصعب علي أن أقرر أو أحدد رائي في الأشياء

٠ أنا بأقرر أو أحدد رأيي في الأشياء بسهولة

- ٠ أنا شكلي كويس
  ١ فيه بعض الحاجات مش كويسة في شكلي
  ٢ أنا شكلي مش كويس أو وحش

- ٢ بأضغط على نفسي طول الوقت علشان أعمل واجبات المدرسة
  ١ بأضغط على نفسي أكثر من مرة علشان أعمل واجبات المدرسة
  ٠ واجبات المدرسة مش مشكلة كبيرة بالنسبة لي

**تذكر أنك بتوصف حالتك في الأسبوعين الأخريين**

- ٢ كل ليلة بيبقى صعب علي أنام
  ١ في ليالي كثيرة بيبقى صعب علي أنام
  ٠ أنا بأنام كويس جدا

- ٠ بأشعر أحيانا أني مجهد أو تعبان
  ١ بأشعر في أوقات كثيرة أني مجهد أو تعبان
  ٢ بأشعر طول الوقت بالتعب أو الإجهاد

- ٢ في أغلب الأيام بيبقى ما عنديش نفس للأكل
  ١ في أيام كثيرة بيبقى ما عنديش نفس للأكل
  ٠ أنا بأكل كويس جدا

- ٠ أنا مش قلقان من أي ألام أو أوجاع
  ١ في مرات كثيرة بأبقى قلقان من بعض الآلام و الأوجاع
  ٢ طول الوقت بأبقى قلقان من الآلام و الأوجاع
- ٠ أنا لا أشعر بالوحدة
  ١ في أوقات كثيرة بأشعر بالوحدة

٢ طول الوقت بأشعر بالوحدة

- ٢ أنا عمري ما شعرت بالمتعة في المدرسة
  ١ أحيانا أشعر بالمتعة في المدرسة
  ٠ في أوقات كثيرة بأشعر بالمتعة في المدرسة

- ٠ أنا عندي أصحاب كثيرة
  ١ أنا عندي بعض الأصحاب و لكن بأتمنى يكون عندي أصحاب أكثر
  ٢ أنا ما عنديش ولا صاحب

- ٠ عملي المدرسي كويس
  ١ عملي المدرسي مش كويس زي ما كان قبل كده
  ٢ عملي المدرسي وحش قوي في مواد كنت دايما كويس فيها

- ٢ أنا لا يمكن أكون كويس مثل بقية زملائي
  ١ لو أردت, فأني أقدر أكون كويس مثل بقية زملائي
  ٠ أنا كويس مثل بقية زملائي

- ٢ في الحقيقة مافيش حد بيحبني
  ١ أنا مش متأكد أن فيه حد بيحبني
  ٠ أنا متأكد من أن بعض الأشخاص بيحبوني

- ٠ أنا في العادة بأعمل اللي بيطلب مني
  ١ في أغلب الأوقات أنا مش بأعمل اللي بيطلب مني
  ٢ أنا عمري ما عملت اللي بيطلب مني

- ٠ أنا بأنسجم مع الناس
  ١ في أوقات كثيرة باتورط في خناقات
  ٢ طول الوقت باتورط في خناقات

# ***Subjects and Methods***

## I- Study design:

This study is a cross-sectional, case control, observational study.

## II- Site of the study:

The cases were selected from the patients attending outpatient clinic of Department of Neuropsychiatry – Ain Shams University Hospitals. The Department of Neuropsychiatry – Ain Shams University Hospitals is located in Eastern Cairo. It serves as a catchment area of about one third of Greater Cairo population. It serves both urban and rural areas.

## III- Subjects:

One hundred and fifty eight children and adolescents participated in this study; they were organized into two major groups, patient group and control group. All patients were selected during two years interval starting from May 2007 to May 2009.

### A- The patients group:

A sample of one hundred and twenty eight patients attending outpatient clinic of The Department of Neuropsychiatry – Ain Shams University Hospitals, either as new cases or for follow up of their condition.

## 1- Selection of sample:

### i- Inclusion criteria:

The study included Egyptian patients suffering from epilepsy. The sample was subdivided according to International League Against Epilepsy Commission Report ***(Engel, 2001)*** into:

- 61 patients suffering from generalized seizures, included cases with generalized tonic, clonic, tonic-clonic, atonic, absence, or myoclonic seizures.

- 59 patients suffering from focal seizures, included cases with simple or complex partial seizures with or without secondary generalization.

With the following criteria:

a) Children and adolescents diagnosed clinically as non-lesional epilepsy (idiopathic or cryptogenic), in the absence of an acute precipitating factor or a history of prior neurological insult.

b) Age range is between 8-16 years old.

c) Both sexes was included.

Parents should give written consent for their children's participation in the study.

**ii- Exclusion criteria:**

a) Patients with IQ score below 80 were excluded.

b) Patients with neuro-developmental disorders and severe neurological disabilities were excluded.

## 2- Choice of cases:

The cases were selected from either new or follow up cases, who were attending the outpatient clinics, neuropsychiatry department, Ain Shams University Hospitals. They were selected according to the inclusion and exclusion criteria. All cases had the selection criteria were included in the study.

### B- The control group:

The control group consists of thirty Egyptian children and adolescents who have no history suggestive of psychiatric morbidity or mental retardation. Any child with history suggestive of any neurological disease or convulsions of any type was excluded. They were selected to match the patient group for age and sex as far as possible.

## IV-Procedure:

1. An informed consent was obtained from the parents of both patients and controls involved in the study.
2. Study proper: All subjects involved in the study were assessed in the following stages:

**Stage 1:**

Clinical diagnosis of epilepsy including:

A. Thorough neurological evaluation with complete neurological examination.

B. Seizure type was defined using the description of the seizure and the results of EEG.

C. Routine inter-ictal EEG.

D. MRI or CT scans according to the case.

**Stage 2:**

Patients were subjected to IQ assessment using Wechsler Intelligence Scale for Children (WISC) to exclude those with IQ less than 80. This test was applied by a clinical psychologist.

**Stage 3:**

Those who were included in the study were subjected to:

A. Mini International Neuropsychiatric Interview (MINI) for diagnosis of psychiatric disorders.

B. The Benton Revised Visual Retention Test (BVRT) to assess any brain dysfunction. This test was applied by an expert clinical psychologist.

C. Chalfont seizure severity scale to assess the severity of the epileptic seizures.

D. Epilepsy calendar to assess the timing of epilepsy seizures.

**Stage 4:**

According to the results of MINI the patients were subjected to either of the following accordingly:

A) Child Depression Inventory (CDI)

B) Revised Children's Manifest Anxiety Scale (RCMAS)

C) Revised Behavior Problem Checklist (RBPC)

The assessment of each patient consumed around 2-4 hours according to the degree of cooperation of the patient and his family, in addition to the complexity of findings obtained from the assessment. Each patient's assessment was done through 1-2 settings.

During the study period, 128 patients were assessed, 8 were excluded because of low IQ.

# Tools:

## *1) Wechsler Intelligence Scale for Children (Wechsler, 1991):*

The Wechsler Intelligence Scale for Children (WISC) is an individually administered measure of intelligence intended for children aged six years to 16 years and 11 months.

The WISC is designed to measure human intelligence as reflected in both verbal and nonverbal (performance) abilities. In addition to its uses in intelligence assessment, the WISC is used in neuropsychological evaluation, specifically with regard to brain dysfunction. Large differences in verbal and nonverbal intelligence may indicate specific types of brain damage.

The current version of the WISC (the WISC-III) consists of 13 subtests and takes between 50 and 75 minutes to complete. The test is taken individually, with an administrator present to give instructions. Each subtest is given separately. There is some flexibility in the administration of the WISC—the administrator may end some subtests early if the test taker appears to have reached the limit of his or her capacity. Tasks on the WISC include questions of general knowledge, traditional arithmetic problems, vocabulary, completion of mazes, and arrangements of blocks and pictures.

**Verbal IQ**

The child's verbal IQ score is derived from scores on six of the subtests: information, digit span, vocabulary, arithmetic, comprehension, and similarities.

**Performance IQ**

The child's performance IQ is derived from scores on the remaining seven subtests: picture completion, picture

arrangement, block design, object assembly, coding, mazes, and symbol search.

***2) The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998):***

The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies and to be used as a first step in outcome tracking in non research clinical settings. The authors describe the development of the M.I.N.I. and its family of interviews: the M.I.N.I.-Screen, the M.I.N.I.-Plus, and the M.I.N.I.-Kid. They report on validation of the M.I.N.I. in relation to the Structured Clinical Interview for DSM-III-R, Patient Version, the Composite International Diagnostic Interview, and expert professional opinion, and they comment on potential applications for this interview.

Sheehan and Lecrubier, when designed the MINI, their central goals for it were:

- Short and inexpensive tool.
- Simple, clear and easy to administer.
- Highly sensitive i.e. a high proportion of patients with a disorder should be detected by the instrument.

- Specific i.e. have the ability to screen outpatients without disorders.
- Compatible with the international diagnostic criteria, including the International Classification of Diseases (ICD-10) as well as the Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised (DSM-III-R), and later the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-VI).

MINI consists of standardized, structured, closed-ended questions throughout its diagnostic procedure. The DSM-IV and ICD-10 criteria were reframed into standardized questions of MINI. The interviewers read literally these close-ended questions to the interviewed persons. Psychiatric diagnosis was made according to the number of affirmative replies to the specific questions.

As a general rule in the structured diagnostic interviews, there are two screening questions. In the negative, no further questions are asked in that disorder module, and the patient is identified as not having the disorder. If the patient responds positively to one or both of the screening questions, more detailed symptom questions are asked. If these questions suggest the presence of typical case, then further branching leads to questions on the chronology and time frame.

This scale was translated into Arabic language, reliability and validity tests were done for it ***(Ghanem et al., 1999)***.

### *3) Benton Visual Retention Test (Benton, 1963):*

**Description:** The Benton Revised Visual Retention Test is a widely used instrument that assesses visual perception, visual memory, and visuo-constructive abilities. Because it measures perception of spatial relations and memory for newly learned material, it is used in clinical diagnosis of brain damage and dysfunction in children and adults, as well as in research. The Benton, as it is usually called, has three alternate forms, each of which consists of ten designs. In addition, there are four possible modes of administration.

**Scoring:** Test interpretation is based on an assessment of the number and types of errors made, and involves several levels of analysis for diagnostic purposes. The examiner compares the examinee's obtained scores with the expected scores found in the norm tables. When examining the difference between these scores for the number correct, the wider the discrepancy in favor of the expected score, the more probable it is that the examinee has suffered neurological impairment.

**Suggested Uses:** The Benton is recommended for use as part of a neuropsychological battery to assess specific dysfunction.

***4) Children's Depression Inventory (CDI) (Kovacs M, 1980):***

**Description:** The Child Depression Inventory (CDI) is a symptom-oriented instrument for assessing depression in children between the ages of 7 and 17 years. The basic CDI consists of 27 items.

This popular self-report scale measures cognitive, affective, and behavioral signs of depression in school-age children and adolescents. Requiring only a first-grade reading level, the CDI has been extensively used in both clinical and research settings.

The CDI is designed to make quantitative measurements of the following symptoms of depression: mood disturbances; capacity for enjoyment; depressed self-evaluation; disturbances in behavior toward other people; and vegetative symptoms, which include fatigue, oversleeping, having difficulty with activities requiring effort, and other symptoms of passivity or inactivity.

**Scoring:** For each item the child has three possible answers; 0 indicating an absence of symptoms, 1 indicating mild symptoms, and 2, definite symptoms. The total score can range from 0 to 54. A score that falls below a cut-off point, or is 1.0 to 2.0 standard deviations above the mean, is considered to be positive for depression. CDI scores of >14 are conventionally considered a clinically meaningful cutoff score to identify significant depressive symptomatology.

This test was translated into Arabic language, reliability and validity tests were done for it ***(El-Tayeb, 1983).***

***5) Revised Children's Manifest Anxiety Scale (Reynolds and Richmond, 1985):***

**Description**: The Revised Children's Manifest Anxiety Scale (RCMAS) is a self-report instrument designed to measure anxiety for children and adolescents aged 6-19 years. For children over 9 and half years of age, it can be administered in a group situation. For first and second graders the examiner should read the items to the child.

The RCMAS has 37 items divided into four scales:

(a) Physiological Anxiety (10 items; e.g., "Often I feel sick in my stomach."),

(b) Worry/Over-sensitivity (11 items; e.g., "I worry about what is going to happen."),

(c) Social Concerns/ Concentration (7 items; "A lot of people are against me."),

(d) Lie Scale (9 items; e.g., "I never get angry.").

The child responds to each question with a "Yes" or "No" answer. "Yes" indicates the item is descriptive of the child's feelings or behavior.

**Scoring:** The Total Anxiety score is based upon 28 items with 9 items comprising the Lie Scale. The Total Anxiety score and the Anxiety subscale scores are determined by the number of

"yes" responses to the anxiety items. The Lie Score is determined by "yes" responses to the Lie subscale items and is used to determine if the child was making a valid attempt to respond. The three anxiety subscales should be interpreted cautiously and should be used only as an aid in hypothesis generation due to limited reliability levels. The Total Anxiety Score is expressed as a T score (M=50, SD = 10) and the subscales are expressed as scale scores (M=10, SD = 3). Percentile ranks are provided for each of the RCMAS scores. The Lie Scale is a positive feature of the instrument and is designed to detect acquiescence, social desirability, or faking of responses.

This test was translated into Arabic language, reliability and validity tests were done for it ***(El-Nayal and Abd El-Hamid, 1991).***

## ***6) Revised Behavior Problem Checklist (Quay and Peterson, 1987):***

**Description**: The RBPC is used to rate problem behaviors observed in adolescents and young children ages 5-18 years. The six RBPC subscales measure Conduct Disorder, Socialized Aggression, Attention Problems-Immaturity, Anxiety-Withdrawal, Psychotic Behavior, and Motor Tension-Excess.

The RBPC has been used for a wide variety of purposes:

- To screen for behavioral disorders in schools
- As an aid in clinical diagnosis
- To measure behavioral change associated with psychological or pharmacological interventions
- As part of a battery to classify juvenile offenders
- To select subjects for research on behavioral disorders in children and adolescents

**Administration and Scoring**: Administration and scoring are straightforward. Raters respond to the 89 items on the top page of the carbonless Test Booklet. Responses transfer to the bottom sheet, which contains scoring instructions and a scoring key. The RBPC Profile Sheet is used to record the obtained raw and *T* scores and to plot the pattern of the test results.

The Rating Form can be completed by a parent, teacher, or other observer in about 20 minutes. Scoring and profiling take about 10 minutes.

This scale is translated into Arabic language, reliability and validity tests were done for it ***(Abou El-Ela et al., 1998).***

***7) The Chalfont Seizure Severity Scale (Duncan and Sander, 1991):***

Seizure severity needs to be quantified for the purposes of evaluating the efficacy of medical and surgical treatments, and to form part of quality of life measures.

The Chalfont Seizure Severity Scale was deliberately not bound by the current classification of seizure types, but was designed to measure, and to be responsive to, the components of seizures that concern patients and their carers.

The reliability of a scale such as this depends critically on the quality of information obtained. It is essential to have a clear and reliable witness, to have the same witness on subsequent assessments and to be consistent with questions, such as the definition of returning to normal.

The scale scores were heavily influenced by the time to return to normal. This factor was, almost invariably, regarded as the most important by patients. The authors attempted fractionating this factor into 30 minute epochs, but found this to decrease the reliability of the data. The fractionation of scores for the factors: dropping of a held object, falling to the ground, injury, incontinence and automatisms, according to the frequency of their occurrence in a patient's seizures, was found to be a useful sophistication. Otherwise, patients would end up with an unworkable multitude of different seizure types.

The Chalfont Seizure Severity Scale has features of both a patient-based and an observer-based scale. The factors to be

included were obtained by open interview of patients and carers and factor weightings were affected by the views of patients, carers and professionals. The scale is completed by an observer, but responses are patient-determined. The scale was developed at a specialized epilepsy clinic and inpatient assessment unit, but will be readily employed in non-specialized outpatient clinics, and may be completed in a few minutes by a doctor or nurse practitioner.

### *8) Statistical methods:*

Statistical analysis were done by the Statistical Package for Social Sciences (SPSS), version 16. The results were tabulated, grouped and statistically analyzed using the following tests:

a) **Pearson Chi Square Test:** to detect whether there is a significant association between different categorical variables.

b) **Student's t Test:** for comparison between means of the different group of patients.

c) **Spearman Correlation Test:** was used when studying the relationship of quantitative variables simultaneously.

d) **Multiple Logistic Regression Analysis:** used to examine the extent to which a set of variables independently predicts a dependent variable.

e) **Mann–Whitney–Wilcoxon Test:** used to compare two groups for non-parametric data.

f) **P value:** used to indicate the level of significance

- P>0.05: Insignificant
- P<0.05: Significant
- P<0.01: Highly significant
- P<0.001: Very highly significant