INTRODUCTION

Epilepsy is one of the most common neurologic disorders in children, with approximately 5–10 children per 1000 affected ***(Shinnar & Pellock, 2002).***

Children with epilepsy often exhibit numerous developmental neuropsychiatric comorbidities, including autistic spectrum disorders, attention-deficit hyperactivity disorder (ADHD) and tic disorders ***(Lin et al., 2012),*** which can interfere with treatment strategies and reduce their quality of life compared with that of the general population ***(Eddy et al., 2010).***

In one of the most important population-based studies of childhood psychopathology, ***(Rutter et al., 1970)***, found evidence of psychiatric disease in 29% of children with uncomplicated epilepsy and in 58% of children with epilepsy and structural abnormalities of the brain.

It is crucial to develop a better understanding of the burden of neuropsychiatric comorbidities in childhood epilepsy in order to improve the quality of life of those affected and identify the shared neurobiological mechanisms underlying multiple co morbidities ***(Weng et al., 2016).***

A tic is a rapid, involuntary, stereotyped, and non-rhythmic movement or phonic production.

Tic disorders, which include chronic tic disorder and Tourette syndrome (TS), are extremely common in children, with epidemiological studies showing that about 20% of school-aged children exhibit isolated and transient tics ***(Scahill et al., 2014).***

Children with TS exhibit clinical diversity and often suffer from various neurodevelopmental comorbidities, including ADHD, learning difficulties, obsessive-compulsive disorders (OCDs), autistic spectrum disorders, and coexistent psychopathologies such as anxiety and depression, which appear to negatively impact their quality of life more than the severity of their tics ***(Cavanna et al., 2009; Mol Debes, 2013).***

It is reasonable to propose that a correlation exists between epilepsy and tic disorders in children as both may share common mechanisms with the involvement of abnormal cortical-basal ganglion circuit connection and dopaminergic dysfunction ***(Weng et al., 2016).***

Although the pathophysiology that gives rise to the clinical heterogeneity and related neurodevelopmental comorbidities remains unclear, converging evidence suggests that abnormal cortical-basal ganglion circuit connections and dopaminergic systems are involved ***(Jankovic & Kurlan, 2011).*** Substantial evidence from the study of epilepsy also suggests that altered dopaminergic neurotransmission and the

corticostriatal network are involved in the disorder ***(Bozzi & Borrelli, 2013; Cifelli & Grace, 2012)*.**

A study was done in Taiwan investigated the risks of developing tic disorders among children with epilepsy which showed that children with epilepsy, have a significantly increased risk of developing tic disorders, which was 8.70-fold increased risk of developing a tic disorders in patients with epilepsy compared with the controls. They also found that males, sufferers of ADHD, and patients prescribed multiple AED treatments were independent risk factors for the development of tic disorders ***(Weng et al., 2016).***

Recent studies support potential effectiveness of some AEDs for patients with TS, the reviewed data suggest that AEDs could be successful in the treatment of tics by increasing the level of GABA, AEDs may affect thalamocortical connectivity, thereby reducing pathological excitability in cortico-striato-thalamo-cortical pathways which results in abnormal behaviors ***(Cavanna & Nani 2013),*** (***Jankovic et al., 2010)*** have reported an improvement in the control of tics with topiramate.

Overall, studies on levetiracetam reported conflicting results, this may be due to the differences in the duration of the studies, in the sample size, in the presence or absence of associated treatment, and/or in the applied methodology. ***(Cavanna & Nani 2013).***

Among the etiological hypothesis of tic disorders, is an autoimmune response to group A beta hemolytic streptococcal infections and the acronym PANDAS was coined (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection) ***(Swedo, 1994; Garvey et al., 1998).***

AIM OF THE WORK

- The primary aim was to determine the impact of tic disorders on quality of life (QoL) and behavioral functioning in children with epilepsy.
- The secondary aim was to unmask whether ADHD being an epilepsy co morbidity is more common in those with tic disorders or not.
- Lastly to highlight the relationship between ASOT and tic disorders in children with epilepsy.

Chapter 1

EPILEPSY

Epilepsy is defined by the International League Against Epilepsy (ILAE) as "a chronic neurological disorder characterized by recurrent epileptic seizures".

The seizures are caused by sudden, usually brief, excessive electrical discharges in a group of neurones in the brain." Epilepsy refers to a large and diverse group of disorders, which share the tendency to have recurrent epileptic seizures ***(Nirmal &Hutchinson 2013).***

The Commission on Epidemiology of the International League Against Epilepsy has recommended that when a person has his or her first two or more seizures within 24 hours, these seizures should be considered a single event. Epilepsy would be diagnosed only if additional seizures occurred at least 24 hours later ***(Camfield & Camfield, 2000).***

Idiopathic epilepsy:

A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurological signs or symptoms.

These are presumed to be genetic and are usually age dependent ***(Engel, 2001).***

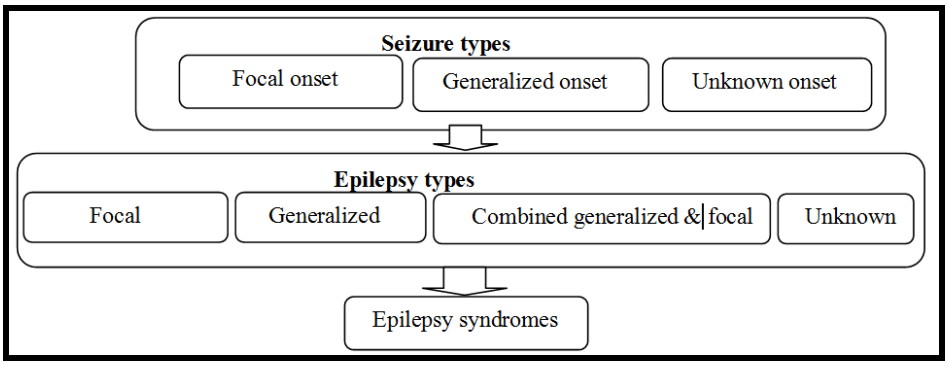

Figure (1): Classification of epilepsy.

Table (1): Types of seizures

Focal onset		**Generalized onset**	**Unknown onset**
Aware	Impaired awareness	Motor Tonic-clonic Other motor	Motor Tonic-clonic Other motor
Motor onset Non motor onset		Non motor(Absence)	Non motor
Focal to bilateral tonic clonic			unclassified

(Scheffer et al., 2017)

- **Idiopathic generalized epilepsy:**

1. Childhood Absence Epilepsy.
2. Juvenile absence epilepsy.
3. Juvenile Myoclonic Epilepsy.
4. Generalized Tonic-Clonic Seizures Alone.

There are no approved ILAE epilepsy syndromes ***(Scheffer et al., 2017).***

Self-limited focal epilepsies:

There are several self-limited focal epilepsies, typically beginning in childhood.

1. The most common is benign epilepsy with centrotemporal spikes.
2. Occipital epilepsies of childhood, with the early-onset form described by Panayiotopoulos and the late-onset form by Gastaut.
3. Other self-limited frontal lobe, temporal, and parietal lobe epilepsies have been described with some beginning in adolescence and even adult life ***(Scheffer et al., 2017).***

Epidemiology:

Epidemiology of idiopathic epilepsy:

Population-based studies have found a slight predominance of focal seizures as compared with generalized seizures.

Only about a third of children with epilepsy can be classified as having a specific epilepsy syndrome ***(Camfield & Camfield, 2015).***

The percentage of idiopathic epilepsies in some cohort studies ranges from 30% ***(Berg et al., 1999)*** to 49% ***(Freitag et al., 2001).***

Epilepsy with centrotemporal spikes is one of the most common epilepsy syndromes in childhood representing 9.6% ***(Berg et al., 1999)*** to 22% ***(Freitag et al., 2001)*** of childhood-onset epilepsy.

The incidence of this syndrome is estimated to be 10/100 000 children per year ***(Berg et al., 2013).***

The incidence of childhood absence epilepsies has been reported to range from 0.7 to 8 per 100 000 and the prevalence from 0.1 to 0.7 per 1000 persons; its frequency in one cohort was reported as 12% ***(Berg et al., 1999).***

Girls are more commonly diagnosed with childhood absence epilepsy ***(McHugh & Delanty, 2008).***

The incidence of JME has been estimated at around 1/100 000 persons; the prevalence ranges from 0.1 to 0.2 per 1000 and its frequency in large cohorts is estimated to range from 5 to 10% ***(Jallon and Latour, 2005).***

The etiology of idiopathic epilepsy can be:

1. Genetic (including epilepsies formerly termed ‘idiopathic’).
2. Unknown.

The cause of epilepsy varies with age. In infancy, perinatal and congenital (including genetic) factors predominate.

Genetic epilepsies are common in later childhood and adolescence. Idiopathic epilepsy syndrome represents 40% of childhood epilepsy disorders, however, it was stated that 70% of epilepsy in childhood consists of idiopathic epilepsy syndrome which also known as non-symptomatic epilepsy ***(Hart, 2016).***

Mechanism and pathophysiology of seizures:

Seizures result from inherent neuronal membrane instability caused by excessive CNS excitation, inadequate CNS inhibition, or a combination of the two.

Simply, a seizure starts when CNS excitation outweighs CNS inhibition which results in prolonged membrane depolarization and ends when the CNS inhibitory systems outweigh the excitatory systems ***(Riviello, & Scott, 2014).***

Cell depolarization results in sodium ion influx which lowers the RMP and causes depolarization.

If depolarization is excessive, an epileptic discharge is generated.

Maintaining the RMP is dependent on the Na-K ATP pump.

Acute neurologic insults, such as hypoxia, ischemia, or hypoglycemia, result in failure of the Na-K membrane pump,

with the inability to restore the RMP and excessive depolarization.

An excess of excitatory neurotransmitters results in excitotoxicity.

Calcium and magnesium inhibit sodium influx.

So excessive Na influx occurs with hypocalcemia or hypomagnesemia, resulting in increased excitability ***(Castilla et al., 2006).***

On the other hand, GABA (g-aminobutyric acid) is the main inhibitory neurotransmitter found in the CNS.

Activation of the GABA-A receptor subtype is responsible for neuronal inhibition.

There is also evidence to suggest that impaired GABA-A receptor function can lead to certain inherited or acquired epilepsies.

Thus, lack of GABA-mediated inhibition along with excessive neuronal excitation are the critical mechanisms of epileptogenicity ***(Kandula, 2009).***

About 40% of patients suffering from epilepsy have a genetic background that contributes to the aetiology of epilepsy ***(Gardiner, 2000).***

Most familial epilepsies like juvenile myoclonic epilepsy, childhood absence epilepsy, and benign childhood epilepsy with centrotemporal spikes have a complex mode of inheritance resulting from the interaction of several loci together with environmental factors ***(McNamara, 1999).***

Nerve cell membranes in epileptics are unstable; during seizures, stored intracellular calcium (Ca2) is released and moves toward inner cell membranes, binding to Ca2-receptive proteins, causing protein conformational changes. These changes trigger transmembranal Ca2, potassium (K), and sodium (Na) channels to remain open, potentiating excitation ***(Pizzorno et al., 2016).***

Diagnosis:

A. History and neurological examination:

Epilepsy is a clinical diagnosis, the most important tool for the accurate classification and optimal diagnosis is the clinical interview.

This should cover seizure-related information, such as subjective and objective ictal symptomatology, precipitation and frequency of seizures, history of seizures in first-degree relatives, and also information relevant for etiology, such as complications during pregnancy and birth, early psychomotor development, and history of brain injuries and other disorders of the central nervous system ***(Schmitz, 2002).***

Other important information that should be obtained refers to doses, side effects, and efficacy of previous medical or nonmedical treatment; evidence of psychiatric complications in the past; and psychosocial parameters ***(Schmitz, 2002).***

The neurological examination may reveal signs of localized or diffuse brain damage.

One should also look for skin abnormalities and minor stigmata suggestive of genetic diseases and neurodevelopmental malformations ***(Schmitz, 2002).***

B. Investigation:

- **Blood tests**

Are often normal,However, hyponatraemia, hypoglycaemia, hypocalcaemia, alcohol abuse and hyperthyroidism can sometimes present with seizures, while anaemia can predispose to syncope.

It is therefore appropriate to check full blood count, renal function, blood glucose and calcium concentrations, and liver and thyroid function, particularly if AED treatment is being considered (most AEDs can affect liver function).

An electrocardiogram (ECG) should be carried out in all people suspected of developing seizures: potentially life-threatening cardiac arrhythmias can present as syncope or seizures. ***(Hart, 2016)***

- **Electroencephalogram (EEG):**

The indications for an EEG depend on the study type and clinical context:

Routine outpatient EEG:

- To determine the type of epilepsy (focal vs. generalized onset seizures, specific epilepsy syndrome).
- To prognosticate risk of seizure recurrence (after a first unprovoked seizure or prior to weaning medications).
- For the differential diagnosis of paroxysmal events which could be epileptic or non-epileptic (e.g. syncope, movement disorders, migraine, non-physiological events) ***(Shorvon et al., 2012).***

- **The interictal surface EEG:**

Is still the most important method in the diagnosis and assessment of all types of epilepsy ***(Schmitz*, *2002).***

A normal inter-ictal EEG does not exclude a diagnosis of epilepsy (epileptic abnormalities are only seen on the initial EEG in about 50% of people with epilepsy), but the presence of epileptic abnormalities can support it ***(Hart, 2016).***

Epileptic abnormalities occur in 0.5% of people without epilepsy, but non-specific abnormalities are common.

Epileptic abnormalities present on an EEG carried out after a single seizure, significantly increase the risk of recurrence ***(Hart, 2016).***

- **Ictal EEG:**

Are also required for exact localization of the epileptogenic focus when epilepsy surgery is considered ***(Hart, 2016).***

- **Ambulatory EEG:**
  - To increase the yield to detect interictal epileptiform abnormalities in patients with normal routine EEG.
  - For the diagnostic evaluation of patients with events which are frequent enough and do not require medication tapering.
  - Determine seizure frequency in patients who are unable to report their events (subclinical events, patients unaware of unwitnessed clinical events) to guide treatment and lifestyle restrictions ***(Shorvon et al., 2012).***
- **Inpatient continuous (video) EEG monitoring:**
  - Diagnostic evaluation of patients with intractable seizures for more than 1 year.
  - Rapid treatment changes in patients with poorly controlled seizures.
  - Presurgical evaluation of potential surgical candidates (non-invasive and invasive) ***(Shorvon et al., 2012).***