# Intractable Epilepsy in Pediatric Patients

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# الصــرع المستعصــي عند الأطفال

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# Summary

Epilepsy is a common chronic neurological disorder characterized by recurrent, unprovoked seizures; these seizures are transient signs of abnormal excessive or synchronous neuronal activity in the brain.

About 50 million people worldwide have epilepsy with almost 90% of these people being in developing countries. The annual incidence of epilepsy per 100. 000 population is 86 in the first year of life, 62 at age 1-5 years, 50 at age 5-9 years, and 39 at age 10-14 years.

According to pathophysiology of epilepsy, two sets of changes can determine the epileptogenic properties of neuronal tissue; abnormal neuronal excitability is believed to occur as a result of disruption of depolarization and repolarization mechanisms (excitability of neuronal tissue), aberrant neuronal networks that develop abnormal synchronization of a group of neurons can result in the development and propagation of an epileptic seizure (synchronization of neuronal tissue).

Nowadays, different mutations in genes that control the excitability of neurons have been described in childhood epilepsy.

Epilepsy has a wide range of causes, and indeed almost all grey matter diseases can result in seizures and the most important factor influencing the range of causes is age.

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# List of Abbreviations

**AEDs** : Antiepileptic drugs
**ATL** : Anterior temporal lobe
**ACTH** : Adrenocorticotrophic hormone
**BBB** : Blood brain barrier
**CNS** : Central nervous system
**CP** : Cerebral palsy
**CPS** : Complex partial seizures
**CT** : Computerized tomography
**CSF** : Cerebrospinal fluid
**CC** : Corpus callosum
**CS** : Corticosteroids
**CRH** : Corticotrophin releasing hormone
**DNA** : Deoxyribonucleic acid
**DBS** : Deep brain stimulation
**EEG** : Electroencephalogram
**ECSWS** : Epilepsy with continuous spike wave during slow wave sleep
**fMRI** : Functional magnetic resonance imaging
**FDA** : Food and drug administration
**GABA** : Gamma amino butyric acid
**GABA-A1** : Alpha 1 subunit of GABA-A receptor
**GTC** : Generalized tonic-clonic seizures
**GI** : Gastrointestinal
**HLA** : Human leucocytic antigen
**ILAE** : International League Against Epilepsy
**IEDs** : Interictal epileptiform discharges
**Ig** : Immunoglobulins
**IVIg** : Intravenous immunoglobulins
**IL-1β** : Interleukin-1β
**IQ** : Intelligence quotient
**KD** : Ketogenic diet
**LINAC** : Linear accelerator
**MRI** : Magnetic resonance imaging
**MRS** : Magnetic resonance spectroscopy
**MEG** : Magnetoencephalography
**MTLE** : Medial temporal lobe epilepsy

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|---|---|
| **MTS** | : Mesial temporal sclerosis |
| **PET** | : Positron emission tomography |
| **P-gp** | : P-glycoprotein |
| **RNS** | : Responsive neurostimulator system |
| **SPS** | : Simple partial seizures |
| **SPET** | : Single photon emission tomography |
| **SPECT** | : Single photon emission computerized tomography |
| **SUDEP** | : Sudden unexplained death in epilepsy |
| **TLE** | : Temporal lobe epilepsy |
| **TCI** | : Transitory cognitive impairment |
| **VNS** | : Vagus nerve stimulation |
| **WHO** | : World Health Organization |

# Introduction

Epilepsy is a common chronic neurological disorder and is estimated to affect about 1% of the population. Although the prognosis for the majority of patient is good; up to 15-35% do not respond to adequate antiepileptic drugs and are said to suffer from medically intractable epilepsy ***(Gupta et al., 2005).***

Intractable epilepsy is defined as a disorder in patient having at least two seizures a month for over two years despite the administration of two first line antiepileptic drugs ***(Gupta et al., 2005).*** In some cases the cause is obvious, for example asphyxial brain damage, congenital infection, or cerebral malformation. However, in many cases this is not so and there is always the question of whether there is an underlying neurodegenerative disease ***(Ashrafi et al., 2007).***

All cases of intractable epilepsy should have a high resolution computed tomography, and ideally, magnetic resonance imaging performed. With these imaging techniques an increasing number of neuronal migration disorders, focal or generalized, are being detected ***(Gomceli et al., 2006).***

A follow up computed tomogram should also be carried out after three to four years if the cause is in doubt, particularly in cases where there is clearly a focal EEG abnormality or seizure pattern. In this way very slow growing tumors, such as oligodendrogliomas, may be detected ***(Sankhla and Khan, 2008).***

Pyridoxine dependency should always be excluded particularly in infantile epilepsy ***(Rajesh and Girija, 2003).***

Patients suffer from intractable epilepsy are at increased risk for cognitive, behavioral, and psychiatric disturbance ***(Ekinci et al., 2009).***

Patients with pharmacoresistant epilepsy have increased mortality compared with the general population but patients with pharmacoresistant temporal lobe epilepsy who meet criteria for surgery and become seizure – free after anterior temporal lobe resection have reduced excess mortality ***(Choi et al., 2008).***

Alternative epilepsy management involves three modalities other than pharmacological agents i. e. AEDs.

Surgical interventions consist of either a resective or disconnective procedures. Resective procedures: These include the different types of lobectomy, tobectomy or hemi-spherectomy. Resective procedures are more likely to result in a cure since they excise the seizure focus itself. Disconnective procedures: These include corpus callostomy and multiple pial transactions and tend to be more palliative rather than curative since they do not eliminate the seizure but interrupt the propagation of the seizures, limiting their generalization ***(Diaz et al., 2008).***

For patients who are not good candidates for epilepsy surgery, there is vagus nerve stimulation - the delivery of

electrical pulses to the vagus nerve in the neck using vagal nerve stimulator. It is a small, battery powered electrical device, and it is implanted below the collarbone. In a cyclical fashion, it delivers intermittent electrical signals to the vagus nerve. These signals are then transmitted to the brain through a poorly understood process, the signals inhibit seizures. Also, the patients can pulse themselves by swiping a magnet across the implant site if they sense the onset of seizure, the resulting signal may abort or shorten the episode. The stimulator has been shown to reduce seizure frequency substantially for some individuals with epilepsy. It is usually intended only as adjunct therapy, and not as a replacement for anticonvulsant medications. This procedure has some side effects like coughing and shortness of breath ***(McBrien and Bonthius, 2008).***

The third modality is the Ketogenic diet which was first introduced in 1921 and still has a role in the management of children with intractable epilepsy. It works against all seizure types, but is most effective in treating epilepsies with myoclonic seizures and is more useful in younger years when the brain's ability to extract ketone bodies is higher. The mechanism of the anticonvulsant action of the ketogenic diet probably relates to the formation of increased cerebral energy reserves. Stable and sustained ketosis seems to be the most important factor. It is important to recall that the diet may have adverse effects, including serious, potentially, life-threatening complications ***(Kang et al., 2007).***

# Aim of the Work

Our aim was to review the pathogenesis, clinical aspects, as well as the therapeutic modalities of intractable epilepsy in children in order to have a better understanding of this grave medical condition.

# Chapter (1)

# Epilepsy

- **Historical aspects:**

In the past, epilepsy was associated with religious experiences and even demonic possession. It was known as the (scared disease) because people thought that epileptic seizures were a form of attack by demons ***(Lammert, 2003-Khwaja et al., 2007).***

However in most cultures, persons with epilepsy have been stigmatized and imprisoned in special places. In Tanzania, as with other parts of Africa, epilepsy is believed by many to be contagious ***(Ikenna, 2007).***

Stigma continues to this day, in both the public and private spheres ***(Valeta and deBoer, 2010).***

Hippocrates wrote the first book about epilepsy almost 2500 years ago, he rejected ideas regarding the divine etiology of epilepsy and concluded that the cause was excessive phlegm that caused abnormal brain consistency, he remarked that epilepsy would cease to be considered divine the day it was understood ***(Goodkin, 2007).***

- **Definition:**

The word epilepsy comes from the Greek word which means (to be seized by forces from without) ***(Aicardi, 1986).***

It is a common chronic neurological disorder characterized by recurrent unprovoked seizures ***(Blume et al., 2001),*** these seizures are transient signs of abnormal excessive or synchronous neuronal activity in the brain ***(Fisher et al., 2005).***

A seizure can be defined as a sudden, transient disturbance of brain function manifested by involuntary motor, sensory, autonomic or psychic phenomena, alone or in combination often accompanied by alteration or loss of consciousness ***(Moe and Benke, 2005).***

Epilepsy is a disorder characterized by the occurance of at least 2 unprovoked seizures 24 hours apart. Some clinicians are also diagnosing epilepsy when 1 unprovoked seizure occurs in the setting of an interictal discharge ***(Fisher and Leppik, 2008).***

- **Epidemiology**

  - **Age specific incidence:**

Epilepsy is more likely to occur in young children, or people over the age of 65, however it can occur at any age ***(Bazil et al., 2005).***

The incidence and prevalence of epilepsy increases in elderly people because hemorrhagic and ischemic stroke, primary or secondary tumors, trauma, dementia, and metabolic disorders occur commonly in this population ***(Blume, 2003).***