

Seizure Disorders: An Overview

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Abstract

INTRODUCTION

Epilepsy is among the commonest disorder encountered by neurologists in their day-to-day practice. It is characterized by the occurrence of at least two or more unprovoked seizures. Depending upon the location and propagation of this hyper-synchronous discharge of cortical neurons the clinical manifestations can be quite myriad. This overview shall cover the classification, pathophysiology, clinical semiology and treatment options available for different types of seizure disorders. The various epileptic syndromes including ones manifesting in the pediatric age group are also discussed.

INCIDENCE AND PREVALENCE OF EPILEPSY

Epilepsy is among the most common neurological disorders encountered by physicians. The incidence and prevalence of epilepsy has varied in different studies from different parts of the world. This is mainly due to differences in inclusion and exclusion criteria, classification and diagnosis. Some patients never seek treatment while others are unaware that they have seizures. Even attentive and doting parents may miss childhood absence seizures while patients with myoclonic jerks of Juvenile Myoclonic Epilepsy (JME) may initially be thought to be jittery or clumsy till a generalized convulsion leads to the correct diagnosis. In most of the studies from the developed countries the overall incidence of epilepsy has been reported to be around 50 cases per 100,000 persons per year (range 40-70 per 100,000 per year). Studies have shown a higher incidence of epilepsy in developing countries as compared to the developed ones- more than 100/100,000 versus less than 50/100,000.

Good epidemiological studies are lacking from the developing and underdeveloped countries of Asia and Africa. A meta-analysis of studies put the overall prevalence rate of epilepsy in India at 5.59 per 1,000 population¹. General prevalence was found to be 11.3 per 1,000 in a

study from Colombia with little variation among regions². A house-to-house cross-sectional population study of epilepsy from Pakistan on 24,130 individuals found an age-specific prevalence rate of 9.99 per 1,000 (14.8 per 1,000 in rural and 7.4 per 1000 in urban areas)³. Another epidemiological study of epilepsy in young Singaporean men indicated a lifetime prevalence of 4.9/1000 males by age 18 years⁴.

Various factors influence the incidence and prevalence of seizures. With more people living well into their 80's in the West, cerebrovascular disease (stroke) is becoming an increasingly common cause of seizures while in developing countries like India neurocysticercosis is the most common cause of acquired epilepsy in the younger age groups.

CLASSIFICATION OF EPILEPSY AND EPILEPSY SYNDROMES

The International League Against Epilepsy (ILAE) classification (1981) is based on clinical semiology and EEG characteristics and not on pathophysiology or anatomical correlates. Under this scheme, seizures were classified as follows:

1. Partial seizures/ focal seizures
 - a. Simple Partial Seizures (no impairment in consciousness)
 - a. with motor symptoms or signs
 - b. with sensory symptoms
 - c. with autonomic manifestations
 - d. with psychic manifestations
 - c. Complex Partial Seizures also called temporal lobe seizures (have impairment in consciousness): can be complex partial

at onset or be simple partial at onset followed by impairment in consciousness.

d. Partial seizures with secondary generalization

- a. simple partial seizures with secondary generalization
- b. complex partial seizures with secondary generalization
- c. simple partial evolving to complex partial seizure followed by secondary generalization.

3. Generalized seizures

- a. Absence or Petit Mal seizures
 - a. Typical Absence seizures
 - b. Atypical Absence seizures
- c. Tonic-clonic seizures
- d. Atonic seizures
- e. Clonic seizures
- f. Tonic seizures
- g. Myoclonic seizures
- h. Myoclonic absence seizures
- i. Myoclonic atonic seizures
- j. Reflex seizures in generalized syndromes

5. Unclassified seizures

- a. febrile convulsions

7. Continuous seizures (status epilepticus)

- a. Generalized status epilepticus
 - a. Generalized tonic-clonic status epilepticus
 - b. Generalized Absence/ Petit Mal status epilepticus
 - c. Clonic status epilepticus

d. Tonic status epilepticus

e. Myoclonic status epilepticus

c. Focal status epilepticus

- a. Epilepsia partialis continua
- b. Psychomotor (limbic) status
- c. Continuous aura (aura continua)
- d. Hemiconvulsive status with hemiparesis

9. Reflex Epilepsies

- a. Photosensitive/ visual sensitive epilepsy (flickering lights and other visual patterns)
- b. Music epilepsy
- c. Eating epilepsy
- d. Hot water epilepsy
- e. Startle epilepsy
- f. Reading epilepsy

11. Epilepsy Syndromes

- a. Childhood epilepsy syndromes (benign)
 - a. Benign familial neonatal seizures
 - b. Benign familial and non-familial infantile seizures
 - c. Benign childhood epilepsy with centrotemporal spikes (Benign Rolandic Epilepsy)
 - d. Early onset benign childhood occipital epilepsy (Panayiotopoulos type)
 - e. Late onset childhood occipital epilepsy (Gastaut type)
 - f. Benign myoclonic epilepsy of infancy
 - g. Childhood absence epilepsy

c. Childhood epilepsy Syndromes
(malignant/poor prognosis)/ Catastrophic
childhood epilepsies

- a. Ohtahara syndrome
- b. West Syndrome
- c. Lennox-Gastaut Syndrome
- d. Early myoclonic
encephalopathy of childhood
- e. Dravet's syndrome
- f. Progressive myoclonic
epilepsies

13. Unclassified

- a. Landau-Kleffner Syndrome
- b. Epilepsy with continuous spike and wave
during slow wave sleep

Adult Epilepsy Syndromes

1. Juvenile Myoclonic Epilepsy
2. Juvenile Absence Epilepsy
3. Mesial temporal lobe Epilepsy with hippocampal
sclerosis
4. Autosomal dominant nocturnal frontal lobe
epilepsy

GENERALIZED SEIZURES

Generalized seizures affect both the cerebral hemispheres right from the onset of the seizure. Thus they are associated with loss of consciousness which may be very brief as in absence seizures or more prolonged leading to loss of body tone. They can be further subclassified on the basis of the clinical semiology as generalized tonic-clonic, generalized tonic, generalized clonic, atonic, myoclonic or absence seizures. A generalized tonic-clonic seizure involves loss of consciousness followed by tonic posturing of the arms and legs. Rhythmic in-phase clonic jerks are then seen and the patient may bite his tongue. Bladder incontinence may occur in either the tonic or the clonic stage of the seizure. As the seizure ends the patient is noted to have drooling from the mouth, sonorous respirations and usually falls asleep.

Electrographically generalized tonic-clonic seizures are characterized by an abrupt change in the background EEG and the appearance of generalized sharp waves which increase in frequency and then evolve to spread over the entire hemispheres. As the clonic jerks start the EEG usually is distorted by superimposed muscle and motion artifact. Following seizure offset diffuse attenuation and slowing is noted and then the EEG slowly reverts to its pre-ictal pattern.

ABSENCE SEIZURES

Childhood absence seizures usually start at the age of 3-5 years and remit by 12-15 years of age. Clinically these seizures may be very subtle and may be missed by even attentive and dotting parents. Usually the child first comes to medical attention due to complaints of day-dreaming or staring at school resulting in poor school performance. The inter-ictal and ictal EEG is characterized by 3 Hz generalized spike and wave discharges with an abrupt onset and offset and a normal background. No post ictal slowing or attenuation of the EEG record is noted. Duration of inter-ictal discharges varies but is usually 3-5 seconds. As the duration of the discharge increased clinical manifestations of staring and automatisms are noted. There is no post-ictal confusion and the child is immediately back to normal once the seizure ends. Childhood absence epilepsy may have significant effects on the psychosocial development of the child and hence treatment is warranted. Treatment with ethosuximide, valproic acid or lamotrigine is efficacious.

MYOCLONIC SEIZURES

Myoclonic seizures are characterized by sudden shock like movements involving the arms and legs or the entire torso. The jerks may at times be so violent so as to throw the patient off balance. Myoclonic jerks are an integral part of Juvenile Myoclonic Epilepsy (JME) Syndrome. JME is characterized by multiplicity of seizure types including absence seizures, generalized tonic-clonic convulsions and myoclonic seizures. The history of myoclonic jerks may not be volunteered unless specifically asked for and it is usually the generalized convulsion which first brings the patient to medical attention. Electrographically these seizures are characterized by generalized spike and wave and polyspikes and wave discharges which are time-locked to the jerks. There is usually a clustering of these myoclonic jerks in the early hours of the morning after the patient wakes up. JME has a good prognosis and the seizures are readily controlled by valproic acid.

As against JME, the progressive myoclonic epilepsies are characterized by progressive neurological impairment and a poor prognosis. The various progressive myoclonic epilepsies include:

1. Early myoclonic epilepsy of infancy
2. Dravet's syndrome
3. Unverricht- Lundborg disease (Baltic myoclonus)
4. Lafora disease

ATONIC SEIZURES

As the name suggests, atonic seizures are characterized by loss of muscle tone. They have also been called drop attacks or akinetic seizures. The person may drop things or fall to the floor but atonic seizures may be more subtle and may involve just the drooping of the eyelids or the head may nod. These seizures usually begin in childhood but may persist into adulthood. While atonic seizures are classified among generalized seizures, ictal atonic events have also been recognized in focal seizures such as that of frontal origin and negative myoclonus. Atonic seizures are classically seen as one of the seizures in Lennox Gastaut syndrome.

The ictal EEG is characterized by a generalized high amplitude spike or polyspike and wave discharge followed by diffuse attenuation. Other patterns described include low or high voltage fast activity or a burst of polyspikes. Video EEG may be of exceptional help in separating atonic seizures from drop attacks of non-epileptic origin.

PARTIAL SEIZURES

Simple Partial seizures are characterized by no impairment in consciousness. They may either be motor characterized by clonic movements or stiffening of an arm or leg. The seizure may spread further to involve adjacent body parts a phenomena called the Jacksonian march.

COMPLEX PARTIAL SEIZURES

Complex Partial seizures are among the commonest seizures encountered in the adult population. They are characterized by an impairment in consciousness during the ictal event usually followed by post-ictal confusion. In as many as 55-65% of patients the seizures are preceded by auras which may give an indication to the location of seizure focus. Special sensory auras like visual, gustatory and vertiginous have been more frequently described in extratemporal epilepsy while viscerosensorial and experiential auras occur

in temporal lobe epilepsy. Feelings of fear and dread have been reported with seizures originating from the mesial temporal structures. Olfactory auras though rare may indicate pathology of the amygdala and hippocampus⁵. A neuroimaging study ideally a MRI with thin coronal cuts through the temporal lobe should be performed in every patient who has experienced a complex partial seizure especially new onset seizure in the older age group to detect focal space occupying lesions. Inter-ictal EEG may reveal epileptiform sharp waves and spike and wave discharges and thus the site of the seizure focus. A negative inter-ictal EEG does not exclude the diagnosis of epilepsy. In cases where the EEG is negative but clinical suspicion for seizures is high, prolonged video-EEG monitoring may be useful. Ambulatory EEG may be used in some instances but is not as sensitive as video-EEG monitoring with the studies frequently contaminated by significant motion and muscle artifact making interpretation of the record difficult. Further seizure semiology cannot be determined in an ambulatory study.

Mesial temporal sclerosis (MTS) is the most common pathologic substrate found in the majority of the temporal lobectomy specimens obtained in connection with temporal lobe epilepsy surgery. Classic Ammon horn sclerosis involves neuronal loss restricted to the CA1 (Sommer sector) and CA4 fields while in total Ammon horn sclerosis neuronal loss is seen in all the zones of the hippocampus (CA1-CA4). MRI diagnosis of MTS is based on occurrence of hippocampal atrophy on T1 weighted images or an increase in the mesial temporal signal intensity on fluid-attenuated and inversion recovery sequences (FLAIR) or T2 sequences. Whether MTS is the cause or the effect of long term seizures is still not known. MRI detected evidence of MTS has been recently reported in patients with sporadic benign temporal lobe epilepsy⁶. Patients with temporal lobe epilepsy due to MTS usually have medically intractable seizures. They should be given a short trial of standard frontline anti-epileptic drug therapy and if they fail to have an adequate response should be worked up for epilepsy surgery.

Surgical outcomes after temporal lobe surgery vary. In an analysis of outcomes in 126 children who underwent temporal lobe surgery for intractable epilepsy, Benifla et.al found an Engel Class I or II outcome in 74% of the patients. Patients with temporal lobe lesions [low-grade brain tumors like ganglioglioma and astrocytoma in 65 (52%), cavernous malformations in 4, MTS in 16 (13%), astrogliosis in 15

(12%), and cortical dysplasia in eight (7%)] had better outcomes compared with those without lesions.

Complications in the form of contralateral homonymous hemianopsia, dysphasia, and infection were reported in 5% of patients. Twelve of their patients had a second temporal lobe procedure for intractable recurrent seizures⁷. Grivas et.al reported their series of 52 patients over the age of 50 years. 40 underwent amygdalohippocampectomies (33 for hippocampal sclerosis, 7 for mesiotemporal lesions). Five lateral temporal lesionectomies plus amygdalohippocampectomy, and seven anterior temporal lobectomies were performed. The mean follow up period was 33 months and the results were compared with a younger cohort operated in the same time period. 37 older patients attained complete seizure control (71% class I), 10 patients had rare postoperative seizures (19% class II), 4 patients improved > 75% (8% class III) while one patient did not improve (2% class IV). The results did not differ from those in the younger age group. There was no peri-operative mortality and a 3.8% permanent neurologic morbidity (dysphasia, hemianopia and hemiparesis) was reported. Importantly neuropsychological testing revealed low preoperative performances with some further deterioration after surgery⁸. Clusmann et al found that five factors were predictive for good seizure control after temporal lobe surgery: 1) clear abnormality on MR images; 2) absence of status epilepticus; 3) MR imaging-confirmed ganglioglioma or dysplastic neuroepithelial tumor (DNT) 4) concordant lateralizing memory deficit; and 5) absence of dysplasia on MR images⁹.

EPILEPSY SYNDROMES OF CHILDHOOD

1. Benign Rolandic Epilepsy: also called benign childhood epilepsy with centrotemporal spikes is an idiopathic age and localization related epileptic syndrome seen in children aged 5-15 years. Age of onset is usually between 4-11 years. Seizures most commonly occur at night when the child is sleeping and clinically have features of partial seizures involving the area around the Rolandic sulcus. Seizures typically are brief hemifacial seizures associated with speech arrest and drooling with preservation of consciousness. At times they may lead to secondarily generalized convulsions. Somatosensory aura may be present but post-ictal confusion is absent. Inter-ictal EEG's are characterized by unifocal or bifocal spike and sharp waves with a horizontal dipole in the centrotemporal areas. Sleep and drowsiness activates the epileptiform discharges. As the centrotemporal spikes may be present only in sleep, a sleep recording should be obtained if there is a strong clinical suspicion. Benign

Rolandic epilepsy is thought to have a genetic basis with the EEG marker inherited as an autosomal dominant trait with age dependent penetrance. By the mid-teenage years the seizures usually remit hence anti-epileptic drug therapy is not needed in all patients. If the decision to treat is made, carbamazepine is usually the first choice. Other medications like gabapentin, oxcarbamazepine, clobazam are also effective.

2. Benign Occipital Epilepsy: is an idiopathic partial epilepsy syndrome characterized by visual symptomatology. Inter-ictal EEG shows occipital paroxysmal spike and wave activity which blocks with eye-opening. A genetic etiology has not yet been proven and the syndrome is hard to identify because of the rather non-specific clinical and EEG features. The disorder has been associated with migraine¹⁰. Benign occipital epilepsy is treated with conventional AEDs used to treat partial seizures.

3. Landau-Kleffner syndrome (LKS): also referred to as acquired epileptiform aphasia is characterized by a triad of receptive and expressive aphasia, EEG abnormalities and seizures usually in a previously normal child between the ages of 2-13 years^{11,12}. Language regression leads to a verbal and auditory agnosia and hence regression of developmental milestones. EEG abnormalities are found even in those children without overt seizures and consists of high amplitude epileptiform spikes and wave discharges or sharp waves synchronously in both hemispheres or focally in the temporal or temporo-occipital regions. They tend to abate in rapid eye movement (REM) sleep. Institution of anti-epileptic drug therapy or steroids may stop the seizures but the language and behavioral deficits usually persist. Like in autistic spectrum disorders these children may benefit from intensive language therapy instituted early in the disease course. Guevara-Campos reviewed the patient records of 10 children with LKS in a study from Venezuela. No cause of the disease could be established in any of the patients. Only one patient in their study displayed abnormalities in the MRI of the brain. All patients received adrenocorticotrophic hormone (ACTH)-based treatment, at a dose of 1 IU/kg/day for one month, administered together with antiepileptic drugs (valproic acid and clobazam). Convulsive seizures and epileptic status during slow-wave sleep disappeared in all the patients. Importantly aphasia improved considerably, which meant that all the patients were able to enroll in normal schools¹³.

4. Lennox-Gastaut syndrome: is a childhood epileptic

encephalopathy syndrome characterized by multiplicity of seizure types, mental retardation and a markedly abnormal EEG with slow generalized spike and wave discharges at a frequency of 1.5 to 2 Hz. It may have multiple etiologies (idiopathic or symptomatic). Seizure type may include atypical absences, myoclonic, generalized tonic-clonic and partial. Drop attacks and nocturnal tonic seizures associated with generalized electrodecrement on the EEG are always present. Seizures are intractable and may lead to profound mental retardation. Atonic seizures may result in injury requiring protective head gear (helmets). Seizures are hard to control and no medical therapy gives complete seizure control. AEDs which have been reported to be effective include valproic acid, clonazepam, clobazam, vigabatrin, zonisamide, lamotrigine, topiramate and felbamate ^{14,15}.

NEWER OPTIONS FOR TREATMENT OF EPILEPSY:

1. Vagal Nerve Stimulator (VNS): in 1997 the VNS was approved by the FDA for adjunctive treatment of refractory partial seizures in adults and adolescents older than 12 years. Since then many thousands of people have been treated with VNS. The precise mechanism of action of VNS is still not fully elucidated but it is believed to cause desynchronization of the cortical EEG. It may also increase seizure threshold by causing release of GABA and glycine in the brain. Labar studied the effect of VNS on 269 patients treated for 1 year with no change in AEDs. Improved seizure rates were found between 3 and 12 months. He concluded that seizure rates declined with increasing VNS duration, this decline occurred without AED changes and was independent of VNS stimulation parameters ¹⁶. In another study in patients with refractory seizures the median reduction at 12 months was 45%, and at 12 months 20% of 195 patients had a >75% reduction in seizures ¹⁷.

2. RNS Neuropace system: Clinical trials are currently on to test the RNS Neuropace system. The RNS is placed inside the skull, underneath the scalp. Electrodes are placed within the epileptic focus in the brain and the device is programmed to continuously monitor brain electrical activity (electrocorticogram) and detect seizures. Once a seizure onset is detected, the machine delivers an electrical discharge into the seizure focus with the intention of suppressing the seizure. Such responsive stimulation devices function on a closed loop system and have generated much interest and efficacy data is eagerly awaited.

CONCLUSION

Epilepsy is a common neurological disorder with high incidence rates in all countries of the world. Most of the seizures can be readily controlled with conventional anti-epileptic drug therapy. Exciting new developments are underway in the field of epilepsy.

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