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Epilepsy Affecting Women Whole Life- A Review

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ABSTRACT

Epilepsy is a disorder characterized by recurrent, unpredictable seizures. It is a sudden rush of electrical impulse in the brain. The game of hormones in women increases their risk of epilepsy. Population studies have reported the incidence in females, at 41 cases per 100,000 persons per year; though that is less than that for males at 49 cases per 100,000 persons per year. Epilepsy is more prevalent in low socioeconomic status groups. Adults have 10-fold higher incidence and prevalence of epilepsy than the general US population. Socioeconomically deprived PWE, especially young adults, die 17 years prematurely. By comparison, daily cigarette smoking shortens life by a decade. Eclampsia is the onset of seizures (convulsions in women with preeclampsia). Pre-eclampsia is a disorder of pregnancy in which there are high blood pressure and either large amount of protein in the urine or the organ dysfunction. Onset may be before, during, or after delivery. Seizures are a tonic-clonic type and typically last about a minute.

INTRODUCTION

Epilepsy is a group of disorders which is characterized by sudden seizure activity which may be recurrent and unpredictable [1]. A sudden rush of electrical activity in the brain is called seizures [2]. The seizure is a temporary physiological dysfunction of the brain, where neurons will provide excessive electrical discharge [1]. Epilepsy is the fourth most common neurological disorder and affects people of all ages. Mild seizures are difficult to recognize. It can last up to a few seconds during which patient may lack awareness. Stronger seizures can cause spasms and uncontrollable muscle twitches and can last a few seconds to minutes. During a stronger seizure people become confused or lose consciousness afterward patient, may have no memory of it happening.

There are two main types of seizures:

1) Focal or partial seizures: Affects just one Part of a brain. Partial (focal) seizures occur when this electrical activity remains in a limited area of the brain.

Synonyms: Jackson seizures; seizures-partial (focal); temporal lobe seizures; epilepsy-partial seizures [3]. The seizures can sometimes turn into generalized seizures, which can affect the whole brain. This is called a secondary generalization.

Partial Seizures can be divided into 2 types:

a. Simple, not affecting awareness or memory.

b. Complex, affecting awareness and memory of events before, during and immediately after the seizures, and affecting behavior.

Symptoms: Abnormal muscle contraction, Lip smacking, abnormal sensations such as numbness, tingling, crawling sensation, Hallucinations, Flushed face, Rapid pulse.

Generalised seizures: Affects both cerebral hemispheres (sides of the brain) from the beginning of the seizures [4]. Generalised seizures are divided into 6 types [5].

Tonic-clonic seizures, Tonic seizures, Clonic seizures, Myoclonic seizures, Absence seizures, Atonic seizures.

Tonic-Clonic Seizures (Grand mall seizures): Tonic-clonic seizures are most common and best-known type of the generalized seizures. They begin with stiffening of the limbs, followed by jerking of limbs and face (clonic phase).

Tonic Seizures: Tonic seizures are characterized by decreased breathing, cyanosis of lips.

Clonic Seizures: This type of seizures last less than a minute. Generally, begin with jerks of limbs and face.

Myoclonic Seizures: Myoclonic seizures are rapid; usually occur at the same time on both sides of the body.

Atonic Seizures: Atonic seizures produce an abrupt loss of muscle tone. People experience sudden collapse with force. Atonic seizures can result in injuries to the head and face.

Synonyms: Drop attacks; Astatic (or) akinetic seizures.

Absence Seizures (Petit-mall): Petit-mall seizures are lapses of awareness, sometimes with starting, that begins and ends abruptly.

Absence seizures are more common in children {4-12 years} than in adults. EEG (Electroencephalography) pattern of diffuse spike –wave is closely correlated with absence seizures [4].

Women's Health and Epilepsy:

Fluctuating hormones makes epilepsy more vulnerable in women. Population studies have reported the incidence in females, at 41 cases per 100,000 persons/year .though that is less than that for males at 49 cases per 100,000 persons per year [6]. As these higher rates in males may be attributable to the higher frequency of some major etiology of seizures in men (e.g.: cerebrovascular diseases, head trauma, alcohol-related seizures), it may be that increasing result in less difference between the sexes. Although most epilepsy syndromes are equally or more commonly found in males than in females, Childhood absence epilepsy and the syndrome of photosensitive epilepsy are most common in females [7]. In addition, some genetic disorders with associated epilepsy e.g. Rhett syndrome and Aicardi syndrome and eclamptic seizures in pregnancy can only occur in females.

Sex Hormones and Epilepsy:

Cortical excitability is known to be affected by the pituitary and gonadal hormones. Oestrogens can activate seizure and to the cerebral cortex on infused intravenous.

Catamenial Epilepsy: It is a general term applied to any exacerbation of seizures with the menstrual cycle. Herzog *et al*. (1997) described 3 patterns of hormonally based catamenial epilepsy [8]. Significantly higher numbers of seizures were found when estrogen increased faster than progesterone, pre-menstrually (catamenial type 1) and pre-ovulatory (catamenial type 2). In patients with an ovulatory cycle, seizures more commonly occurred in the second half of the cycle (catamenial type 3) when progesterone was lower than normal due to fracture to develop a corpus luteum [8]. Synthesised novel neuro-steroids such as ganaxolone, a synthetic analog of allopregnanolone, have proven promising but also have prohibitive production costs [9].

Infertility and Epilepsy:

Overall, women with epilepsy have lowered fertility compared with women in general population [10]. Menstrual disorders are estimated to occur in 1-3 women with epilepsy compared with 1-7 in the general population [11]. Seizures themselves can result in abnormal reproductive hormones variations. Fluctuations of Luteinizing hormone (LH) and pulsatile release of prolactin and sex steroids have been observed in temporal relation to some seizures [12]. Some studies have indicated that reproduction rates in married women with epilepsy are not less than that those in married women without epilepsy. Although marriage rates are lower and occur at older ages, when fertility may be less for other reasons [13]. PCOS has been reported in 41% women with Idiopathic generalized epilepsy and in 26% of women with localization-related epilepsy [14].

Contraception and Epilepsy:

Women taking cytochrome p450 enzyme-inducing Anti-epileptic drugs have a potential 6% failure rate per year for oral contraceptive pill [15]. The more potent enzyme inducers (Carbamazepine, Phenytoin, Phenobarbital, and Primidone) are the most likely to interfere with contraception.

Pregnancy and Epilepsy:

Approximately, 35% of women with epilepsy have more seizures during pregnancy, 10% have fewer, and 55% remains the same [16]. Physiologic changes of pregnancy that can alter both seizure threshold and ADE pharmacokinetics include increases in sex hormones, increased volume of distribution, altered plasma protein binding, decreased gastric motility, increased cardiac output, increased renal elimination and altered hepatic metabolism. The fetal may also be inadequate to process these drugs which circulate from the mother through the placenta [17].

Symptoms: Dizziness, Headache, Changes in mood or energy levels, Fainting**,** Confusion**,** Memory loss.

Epidemiology:

The National Institute of Neurological Disorders and Stroke (NINDS) estimates affect 1% of the United State population (about 2.5 million people). It is estimated that about 1/3, 1/2 of the women with epilepsy will have more frequent seizures during epilepsy.

Anti-convulsants medicines are the main reason for the increase in seizures. The action of AED changes during pregnancy. There is a need to change the medication during pregnancy [2]. About 25-30% of women have increased seizures during pregnancy; whereas seizures decrease in a similar number increased seizure activity may result in from either direct effect on seizures threshold or reduction in AED concentration. An increase in clearance has been reported for Phenytoin, Carbamazepine, Phenobarbital, Ethosuximide, Lamotrigine, and Clorazepate. Protein binding also may be altered. The altered disposition of AED's may begin as early as the first 10 weeks of pregnancy and may take up to 4 weeks postpartum to return to normal.

Signs and Symptoms:

Seizures: The most common type is convulsive (60%); 1/3rd of these, begin as generalized seizures from the start affecting both sides of the brain, remaining 40% of seizures are non-convulsive which begin as focal seizures [5]. An example of this is the absence seizure, which presents as a decreased level of consciousness and usually last about 10 seconds [18, 19].

Simple Partial Seizures: [20].

Motor signs include:

1. Alternating contractions and relaxations of muscle groups.
2. Eye movements and turning the head in the same direction.
3. The asymmetrical posturing of the limbs
4. Vocalisation and speech arrest.

Sensory signs:

1. Seeing flashes of lights or colors, illusions, and hallucinations.
2. Hearing humming, buzzing, hissing noises.
3. Experiencing unpleasant odors and tastes.
4. Dizziness, lightheadedness.

Autonomic signs and symptoms: Flushing, Incontinence, Nausea, vomiting, Piloerection, Tachycardia.

Psychic symptoms: Detachment, depersonalization, Dreamy state, Memory distortion, Depression, Elation, Eroticism.

Complex Partial Seizures: Loss of consciousness, Automatisms, Chewing**,** Facial expression of fear, Crying, Wandering**,** Repeated short phrases or swearing, Drop attacks.

Tonic-Clonic Seizures:

Tonic phase consists of Fall**,** Loss of consciousness**,** Yell or "Tonic cry", an extension of arms, legs and face, fingers and jaw clenched, increased blood pressure, Increased bronchial secretion, Apnoea.

Clonic phase consists of muscle relaxes, rhythmic jerks of the body, drooling, biting of tongue, urinary incontinence.

Absence Seizures: Licking the lips, scratching, blank staring, change in facial expression, lack of awareness, responsiveness and memory.

Causes of Epilepsy:

Epilepsy can have genetic and acquired causes [21], Other causes include Serious brain trauma, Stroke, Tumours and problems in the brain, results of the previous infection.

Classification:

In 2011, the ILAE commission for classification of the epilepsies addressed this issue and divided epilepsies into 4 categories and a number of subcategories' reflecting recent technologies and scientific advances [22].

1. Unknown Cause (mostly genetic or presumed genetic origin)

A) Pure epilepsies due to single gene disorders

B) Pure epilepsies with complex inheritance

2. Symptomatic (associated with gross anatomic or pathologic abnormalities).

a. Mostly genetic or developmental causation: Childhood epilepsy syndromes, Progressive myoclonic epilepsies, Neurocutaneous syndromes, Other neurologic single gene disorders, Disorders of chromosomal function, Development abnormalities of cerebral structure

b. Mostly acquired causes: Hippocampal sclerosis, Perinatal and infantile causes, Cerebral trauma, tumor/infection, Cerebrovascular disorders, Cerebral immunologic disorders, Degenerative and other neurologic conditions.

c. Provoked (A specific systemic or environmental factors is the predominant cause of the seizures): Provoking factors, Reflex epilepsies.

d. Cryptogenic.

Pathophysiology [23]**:**

a. The seizure originates from the grey matter of any cortical or perhaps subcortical area.

b. Initially, a small number of neurons fire abnormally. Normal membrane conductance and inhibitory synaptic currents break down, and excess excitability spreads, either locally to produce a focal seizure or more widely to produce a generalized seizure.

c. This onset propagates by physiologic pathways to involve adjacent or remote areas. An abnormality of potassium conductance, a defect in the voltage-sensitive ion channels, or a deficiency in the membrane ATPase's linked to ion transport may result in neuronal membrane instability and a seizure.

d. Seizure activity is characterized by paroxysmal discharges occurring synchronously in a large population of the cortical neuron. This is characterized by EEG as a sharp wave or spike.

e. The basic physiology of a seizure episode is traceable to an unstable cell membrane or its surrounding supportive cells.

f. A relative deficiency of inhibitory neurotransmitters such as GABA or an increase in excitatory neurotransmitters such as glutamate would promote abnormal neuronal activity.

g. The normal neuronal activity also depends on an adequate supply of glucose, oxygen, sodium, potassium, chloride, calcium, and amino acids.

h. Systemic pH is also a factor in precipitating seizures.

Prevalence:

Epilepsy is more prevalent in low socioeconomic status groups. Adults have 10-fold higher incidence and prevalence of epilepsy than the general US population. Socioeconomically deprived PWE, especially young adults, die 17 years prematurely. By comparison, daily cigarette smoking shortens life by a decade [24].

Selected morbidities of seizures and chronic epilepsy:

Seizures: Falls and injuries, head trauma, soft tissue injuries, seizures-induced orthopedic disorders, vertebral compression fractures, shoulder dislocation, aspiration pneumonia, burns, motor vehicle accidents.

Epilepsy: Stigma, learning disorders, and academic problems, unemployment and underemployment, osteoporosis (AED induced), progressive cognitive impairment, memory, executive function, attention, psychiatric illness, depressive disorders, anxiety disorders, attention deflect disorder, psychotic disorder, structural progressive brain atrophy.

Diagnosis:

An Electroencephalogram (EEG), CT scan, MRI, Serum Electrolyte, Blood Glucose, Calcium levels.(Misdiagnosis is frequent {occurring in about 5-30cases})[5].

Management:

Non-Pharmacological Management

Diet management: the Ketogenic diet high in fats and low in carbohydrates and protein and thus leads to acidosis and ketosis, No sugars intake, Fluids should be controlled.

Surgery [success rate is between 80-90% of patients.], Implementation of a vagus stimulator [25].

Pharmacological Management:

Barbiturates:

a. Mephobarbitol (mebral) : Usual initial dose-50-100mg/day; maximum daily dose:400-600mg;

b. Phenobarbital: Usual initial dose- 1-3 mg/day (10-20 md/kg/LD); maximum daily dose: 180-300 mg;

Mechanism of Action: It decreases post synaptic excitation, possibly by stimulating post synaptic GABAergic inhibition responses.

Indication: Drug of choice for neonatal seizures but in other situations is reserved for patients who have failed other AED'S.

Drug interaction: Phenobarbital X valproic acid, phenytoin, felbamate, cimetidine, chloramphenicol (reduces the metabolism of phenobarbital), ethanol (increases metabolism of phenobarbital).

Side effects: Ataxia, headache, sedation, metabolic bone disease.

a. Primidone: Usual initial dose-100-125 mg/day; maximum daily dose:750-200mg;

b. Carbamazepine (Tegretol): Initial dose-400mg/day; maximum daily dose: 400-2400mg;

Mechanism of Action: The exact mechanism by which carbamazepine suppress seizures is unknown, although it's believed to act primarily through inhibition of voltage-gated sodium channels [25].

Side effects: Side effects are most common during initiation of therapy and may dissipate with continued treatment [25]. Hyponatremia; blood dyscrasias; diplopia; unsteadiness.

a. Phenytoin (Dilantin): Initial dose- p.o: 3-5mg/kg (200-400mg);maximum daily dose: to: 500-600 mg;

Mechanism of Action: Acts by following mechanisms; alteration of calcium uptake in a presynaptic terminal; influence on calcium-dependent synaptic protein phosphorylation and transmitter release.

Side effects: Lethargy; Cognitive impairment; fatigue; rash; blood dyscrasias; Foliate deficiency; Acne.

a. Diazepam (Valium): Initial dose- po:4-40mg;IV:5-10mg;maximum daily dose:po:4-40 mg;IV:5-30mg.

Special Considerations in Female Patients:

Pregnancy raises several concerns including the possibility of maternal seizures, pregnancy complications, and adverse fetal outcome.

AED'S can cause many teratogenic effects and these teratogenic effects can be prevented by adequate folate intake; therefore, prenatal vitamins with folic acid (~0.4 to 1mg/day) should be given to any women of childbearing potential who is taking AEDS.

Vitamin K (10mg orally given daily during the last month of pregnancy) should be given to the mother in order to prevent coagulopathy {AEDS can also cause neonatal hemorrhagic disorder} [26].

Eclampsia: It is defined as a disorder of pregnancy in which there are high blood pressure and either large amount of protein in the urine or the organ dysfunction [27, 28].

Onset may be before, during, or after delivery. Seizures are tonic-clonic type and typically last about a minute.

Complications: Aspirations**,** pneumonia**,** cerebral haemorrhage**,** kidney failure**,** cardiac arrest.

Eclampsia: It is defined as the onset of seizures (convulsions in women with preeclampsia) [29]. Usual onset after 20 weeks of pregnancy. Prevention with aspirin, calcium supplementation treatment of prior hypertension [30, 31]. Exercise during pregnancy may also be useful in preventing eclampsia. Pre-eclampsia is estimated to affect about 5% of deliveries while eclampsia affects about 1.4% of deliveries [32]. In the developed world, rates are about 1 in 2000 deliveries due to medical care [29]. Hypertensive disorders of pregnancy are one of the most common cause of death in pregnancy [33]. They resulted in 46,900 deaths in 2015 [34].

Signs and Symptoms: Pain around pelvis or abdomen [35], reduced urine, stillbirth, cerebral palsy, hypertension and proteinuria before the onset of convulsion, edema of hands and feet's, nausea, vomiting, headaches, cortical blindness. If multi-organ failure ensues then abdominal pain, jaundice, shortness of breath and diminished urine output, fetus may develop intrauterine growth retardation and with maternal convulsions, bradycardia and fetal distress [36].

Risk factors: Eclampsia tends to occur in first pregnancies and young mothers women with pre-existing vascular diseases (hypertension, diabetes, and nephropathy or thrombophilic diseases such as the antiphospholipid syndrome).

Management:

Non-Pharmacologic Treatment: Eat high- antioxidant foods, consume less salt, take plenty of potassium-rich foods and maintain a healthy weight. Prevent dehydration and fatigue [35].

Delivery: If a baby has not yet been delivered, several steps need to be taken to stabilize the women and deliver her speedily. This needs to be done even if the baby is immature, as the eclamptic conditions are unsafe for both baby and the mother.

Pharmacological Treatment: Magnesium sulfate commonly called as Epsom salt, results in better outcomes than diazepam, phenytoin or a combination of chlorpromazine, promethazine, pethidine [37].

Blood pressure management: Agents for blood pressure control eclampsia are hydralazine and labetalol.

DISCUSSION AND CONCLUSION

To improve the management of epilepsy is a concern for both health professional and people with epilepsy as it has high psychosocial and economic cost [38]. A clinician has to face the challenges which come with the treatment of epilepsy in women as he has to be more thoughtful about the choice of antiepileptic drugs as it may show an effect on the reproductive planning and metabolic health. Careful and frequent assessment needs to be made from menarche onwards [39]. Geriatric women taking AEDS show decline in blood folate levels, to subdue the deficiency folate supplementation (0.4 mg/day) should be taken [40].

During pregnancy frequent AED serum level monitoring should be performed at the beginning of every trimester. AEDS may decrease bone mass density (BMD) which results in osteopenia, osteoporosis, and fractures. Calcium and Vitamin D supplementation should be given at prophylactic doses levels. Should avoid any situations which precipitate seizures (changing of AEDS, sleep deprivation non-compliance etc.). Surgery can be viewed as a major tool in the management of epilepsy in children, which can be best utilized when partial seizures or medical treatment is interrupting the child's development and interpersonal relationships. After surgery, the treatment will be greatly simplified and the seizures will be eliminated insignificant number of cases [41].

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