Section A-Research paper

An Insight about Causes and Diagnosis of epilepsy

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Abstract

Background: The pathophysiology of epilepsy or epileptogenicity occur due to alterations of normal physiological processes, which lead to synchronous and sustained firing of a population of neurons in the brain. Altered excitatory and inhibitory influences predispose to excessive synchrony within neuronal populations. The behavioral manifestations of a seizure reflect the function of the cortical neurons involved in the generation and spread of abnormal electrical activity. Stroke and other cerebrovascular diseases are the most important risk factors for new-onset epilepsy in the elderly, which account for 30%–50% in all identified causes. Post traumatic seizure is defined as a seizure occurring after head trauma which is causally related to the trauma itself. Traumatic brain Injury (TBI), apart from its major morbidity and mortality is a major cause of epilepsy. Malformations of cortical development (MCDs) play a major role in the etiology of epilepsy. One of the MCD subtypes is focal cortical dysplasia (FCD). The disorder is the result of neuronal proliferation and differentiation disruption during brain development. The diagnosis of epilepsy is typically based on the description of the seizure and surrounding events. An electroencephalogram (EEG) and neuroimaging are also usually part of the workup. While figuring out a specific epileptic syndrome is often attempted, it is not always possible. Video-EEG monitoring may be useful in difficult cases. EEG continues to play a central role in diagnosis and management of patients with seizure disorders in conjunction with the new remarkable variety of other diagnostic techniques developed over the last years because it is a convenient and relatively inexpensive way to demonstrate the physiological manifestations of abnormal cortical excitability that underlie epilepsy

Keywords: Diagnosis, seizures, causes, epilepsy

Introduction

Epilepsy is one of the most common neurologic diseases in the world. It affects approximately two million people in the United States and more than 50 million people worldwide, with 16–51 cases of new-onset epilepsy per 100.000 people every year **(1).** The prevalence for active epilepsy was found to be 5.6/1000 in Canada **(2),** and 6.3/1000 in the United States of America **(3).** In Arab countries, the estimated prevalence of epilepsy in children was found to be 3.6-10.5/1000 **(4).**

In Egypt, the lifetime point prevalence of epilepsy among inhabitants of Al-Manial island was 6.9/1000 inhabitants, while the prevalence of active epilepsy was 5.1/1000 inhabitants. The age distribution showed bimodal peaks in adolescents and in elderly with equal sex ratio (6/855 vs 6/896). Focal seizures were the commonest type (58.3%) and the treatment gap was 66.7% **(5).** The prevalence of epilepsy among Fayoum inhabitants was 12/1000, with 95% CI (8.5-16.5)/1000 of the population **(6).**

The pathophysiology of epilepsy or epileptogenicity occur due to alterations of normal physiological processes, which lead to synchronous and sustained firing of a population of neurons in the brain. Altered

excitatory and inhibitory influences predispose to excessive synchrony within neuronal populations. The behavioral manifestations of a seizure reflect the function of the cortical neurons involved in the generation and spread of abnormal electrical activity **(7).** Three key elements contribute to the development of the hyperexcitability needed for epileptogenesis: 1) the capability of membrane in pacemaker neurons to develop intrinsic burst discharges; 2) the reduction of gamma-amino-butyric acid (GABA) inhibition; and 3) enhancement of synaptic excitation through recurrent excitatory circuits (mossy fiber sprouting in hippocampal sclerosis). Although intrinsic membrane hyperexcitability provides a substrate for epileptogenesis, circuit dynamics are more important for paroxysmal electrophysiological tendencies **(8)**.

Causes of symptomatic epilepsy

1-Cerebrovascular diseases:

Stroke and other cerebrovascular diseases are the most important risk factors for new-onset epilepsy in the elderly, which account for 30%–50% in all identified causes. In the acute phase of stroke, epileptic discharges are induced by ischemia, hypoxia, and cerebral edema. Seizures usually occur within the first 48 hours of ischemic stroke, and within hours of subarachnoid hemorrhage**.** In general, seizures may occur at the time of or after stroke, or it may be an early clinical manifestation of cerebrovascular diseases. Studies have reported that the risk of developing epilepsy in the first year after a stroke increases by 20 times **(9).**

The number of lesions, the size of the stroke, and the site are all closely linked to the probability of the occurrence of epilepsy. A 12-year follow-up study shows that visual neglect, dysphasia, and stroke subtype (particularly total anterior circulation infarcts), are predictors of post stroke epilepsy.Hemorrhagic transformation of ischemic stroke is a risk factor for epilepsy, which might be related to the blood–brain barrier disruption. One study has shown that patients with suspected cardio-embolic etiology have almost two times the risk of developing epilepsy compared with those who have vessel thrombosis **(10).**

In addition, there are factors associated with post stroke epileptogenesis including, lifestyle factors (such as, smoking, alcohol use), acute metabolic disturbances (such as, acid-base imbalance, electrolyte imbalance, hyperglycemia), non-central nervous system (CNS) morbidities (such as, diabetes, dyslipidemia, renal insufficiency, hypertension, coronary heart diseases or myocardial infarction), CNS morbidities (such as, early seizures, status epilepticus within 2 weeks post-stroke, depression or use of antidepressants, dementia), pharmacotherapy (including antiepileptic drugs, noradrenergic blockers, noradrenergic agonists, benzodiazepines, voltage-sensitive calcium-channel blockers, statins) **(11).**

The EEG is not consistent in predicting epilepsy after stroke. Lateralized periodic discharges (LPDs), formerly known as periodic lateralized epileptiform discharges (PLEDs) are considered a classic finding in stroke and may be predictive of seizures and may only predict early seizures and not necessarily later epilepsy. The most common finding is slow activity (focal or generalized), which is non-specific and not predictive of seizures. Small vessel and microvascular diseases of the CNS are causes of epilepsy. It is reported that risk factors of cerebrovascular diseases, such as high blood pressure, high cholesterol, and coronary and peripheral arterial disease, are associated with epilepsy, even in the absence of stroke, which is confirmed by radiographic evidence. Cerebral amyloid angiopathy is associated with small vessel diseases, including white matter hyperintensities and cerebral microbleeds; some publications report that epilepsy is primarily related to the presence of lobar hemorrhages, which result from cerebral amyloid angiopathy in the elderly **(12).**

2. Post-traumatic seizures (PTS):

Post traumatic seizure is defined as a seizure occurring after head trauma which is causally related to the trauma itself**.** Traumatic brain Injury (TBI), apart from its major morbidity and mortality is a major cause of epilepsy**,** particularly in young adults**.** Head trauma may be classified as mild, moderate, and

severe. The presence of early seizures in combination with moderate or severe head trauma increases the risk of developing epilepsy. One study in children and young adults has shown that the risk of post-traumatic epilepsy is the highest in the first year, although it remains a high risk in the next ten years or longer **(13).**

Head trauma is a common cause of intractable epilepsy, accounting for 10%–20% of symptomatic epilepsy in the general population and five percent of all epilepsy. Older people are more likely to fall, which may result in serious consequences such as head injury; the risk of post-traumatic epilepsy in people aged 65 years or older becomes higher. Subdural hematoma and post-traumatic hemorrhage are associated with seizures in patients who have experienced traumatic brain injury **{table (1)} (14).**

Table (1): Risk Factors for seizures in patients with TBI **(14)**

Risk factors for early PTS	**Risk factors for late PTS**
Glasgow Coma Scale <10	Early PTS
Penetrating brain injuries	Acute intracerebral hematoma
Acute intracerebral hematoma	Brain contusion
Acute subdural hematoma	Loss of consciousness
Younger age	Post traumatic amnesia lasting >24 hours
Loss of consciousness	Age >65 at the time of injury
Post traumatic amnesia lasting >30 minutes	
Chronic alcoholism	

(PTS): Post-traumatic seizures, (TBI): Traumatic brain injury

3-Mesial temporal sclerosis:

Mesial temporal sclerosis (MTS), also known as hippocampal sclerosis**,** is one of the most common causes of adult-onset epilepsy, especially refractory epilepsy**.** However, it has been found in up to 14% of adults without epilepsy and typical ictal EEG pattern consists of anterior temporal rhythmic theta or alpha activity. The most common magnetic resonance imaging (MRI) finding in MTS, as seen in**,** is hippocampal hyperintensity on T2-weighted sequences such as fluid-attenuated inversion recovery (FLAIR). However, this is not very reliable. Hippocampal atrophy is the most specific finding, usually noted on T1-weighted **{Figure (1)} (15).**

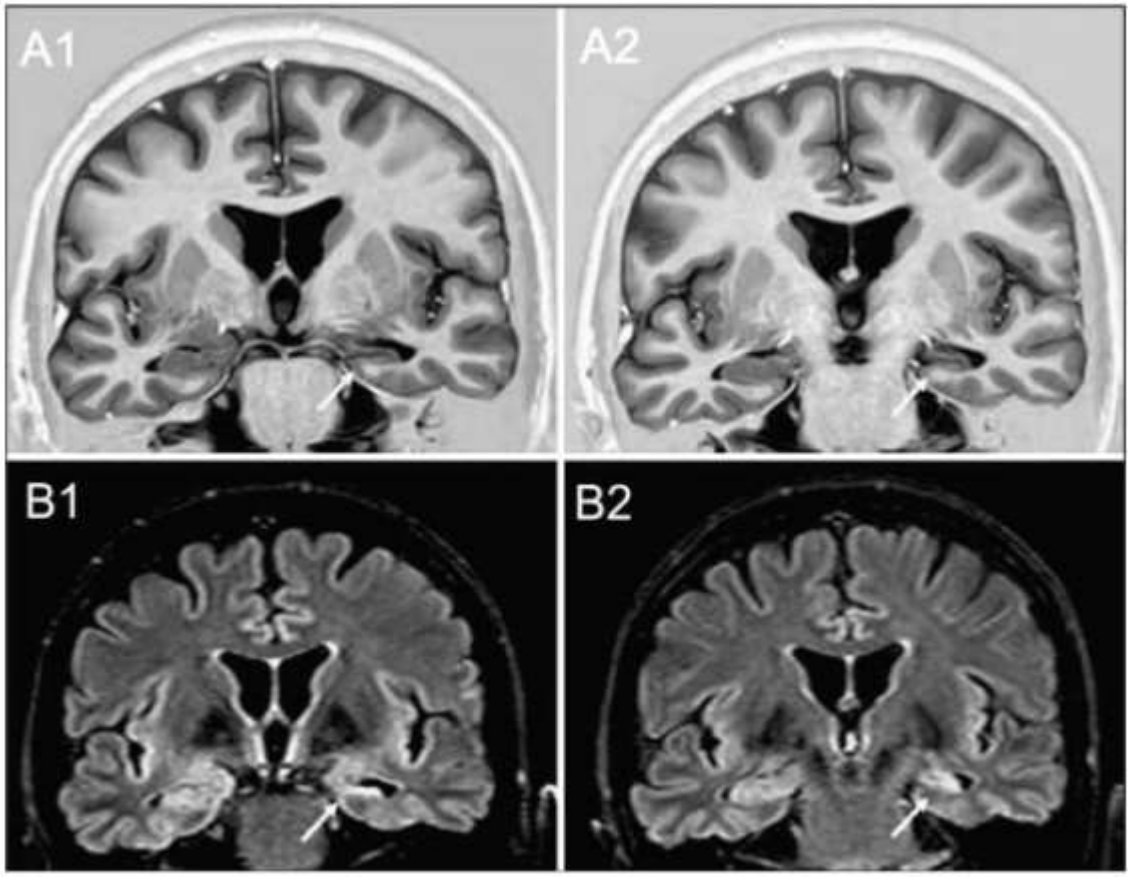

Figure (1) MRI brain coronal T1-weighted inversion recovery (A1 and A2) and T2 fluid-attenuated inversion recovery (FLAIR) images (B1 and B2) from a patient with left mesial temporal lobe epilepsy (TLE) showing signs of left hippocampal sclerosis (arrows): hippocampal atrophy with abnormal shape and hyper intense signal on T2-FLAIR images **(15).**

4-Focal cortical dysplasia (FCD):

Malformations of cortical development (MCDs) play a major role in the etiology of epilepsy. One of the MCD subtypes is focal cortical dysplasia (FCD). The disorder is the result of neuronal proliferation and differentiation disruption during brain development **(16).**

FCD is the second/third most common etiology of medically intractable seizures in adults. Numerous classifications of FCD have been proposed. In general, three types of cortical dysplasia are recognized. Type I focal cortical dysplasia with late onset, is more often seen in adults. Clinical symptoms are more severe in type II of cortical dysplasia usually seen in children. New type III is one of the above dysplasias with associated another principal lesion as hippocampal sclerosis, tumor and vascular malformations or acquired pathology during early life**.** Typical MRI findings include blurred gray–white junction, thickened cortex**.** Many FCDs are subtle or not visible on MRI and may be found on functional imaging **{Figure (2)} (17).**

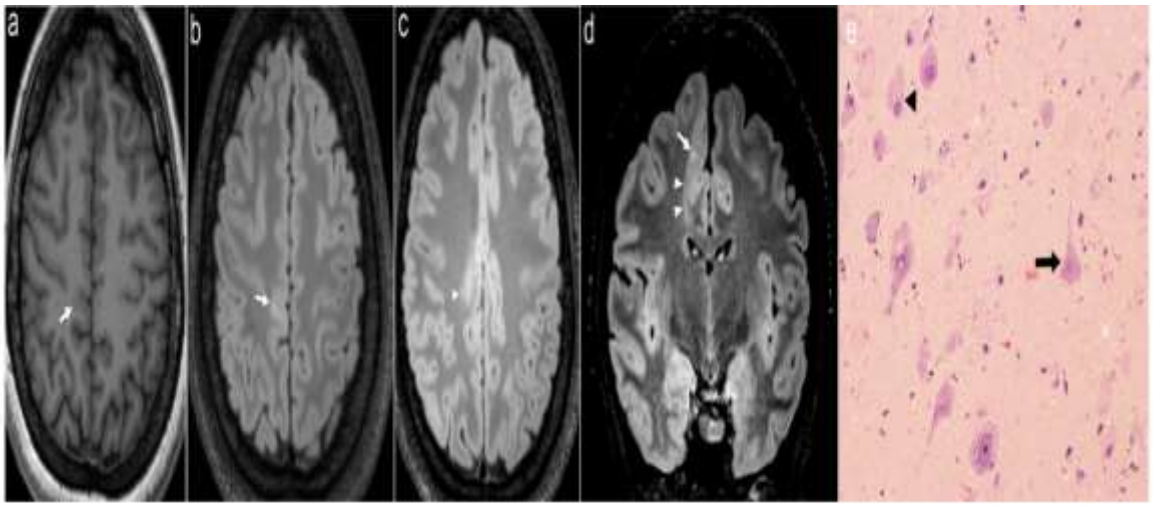

Figure (2): Focal cortical dysplasia. A 28-year-old female with medically refractory seizures since age 4, consisting of left arm tingling and dystonia; EEG suggested midline central origin. MRI was initially interpreted as normal, but reevaluation after knowledge of semiology and EEG findings revealed minimally thickened, hyperintense gyrus with blurred gray–white interface, in the right paracentral lobule (white arrow) on axial T1W (a) and axial FLAIR (b) images. Very subtle radial band (arrowhead) is present on axial FLAIR (c). This was confirmed on an oblique coronal reformatted image (d), showing subtle subcortical hyperintensity (arrow) with a radial band to the ventricle (arrowheads). F-18 FDG-PET also confirmed this abnormal region. (e). Focal cortical dysplasia type IIb in a different patient with seizure onset at age 15 consisted of episodes of flashing lights. A right parietal lesion was resected and showed both dysmorphic neurons (black arrow) and balloon cells with eccentric nucleus (arrowhead) on photomicrograph (original magnification,20×; hematoxylin-eosin (H-E) stain). F-18 FDG-PET, F-18-fluorodeoxyglucose positron emission tomography **(17).**

5-Vascular Malformations:

Epilepsy is most strongly associated with arteriovenous malformations (AVMs) and cavernous malformations (CMs). Developmental venous anomalies (DVAs) are usually incidental findings and not epileptogenic. In most vascular malformations, the surrounding hemorrhage, gliosis, and encephalomalacia are the epileptogenic pathologies **(18).**

5- Causes of cryptogenic epilepsy

Although some of new-onset epilepsies in the elderly show identified etiology, one-third to one-half of geriatric epilepsies still have undetected causes, to date, despite the current advances in technology. Paraneoplastic limbic encephalitis and posterior reversible leukoencephalopathy syndrome are probably the rarest of the unknown causes of new-onset epilepsy in the elderly. Therefore, these rare factors should be taken into account when no identified causes can explain the reason for geriatric epilepsy**.** Immune factors may be potential causes in patients with undetected causes. A study conducted in the United States of America on adult patients (most of whom could be considered elderly) in several intensive care units, highlights the immune origin of the new-onset refractory status epilepticus (NORSE) **(19).**

6- Status Epilepticus (SE)

The International League Against Epilepsy defines SE as abnormally prolonged seizures greater than 5 minutes in the presence of generalized tonic-clonic activity, greater than 10 minutes of focal seizures with impaired consciousness and greater than 10 to 15 minutes in case of non-convulsive seizures **(20).**

The Neurocritical Care Society defines SE as 5 or more minutes of continuous clinical and/or electrographic seizures, or recurrent seizure without recovery to baseline. Status epilepticus results either from failure of the mechanisms responsible for seizure termination or from initiation of mechanisms, which lead to abnormally prolonged seizures. SE can have long-term consequences depending on the type and duration of seizures **(21).**

Status epilepticus may be of nonconvulsive type that may impair consciousness, but not manifest any abnormal bodily movement. This represents an important and potentially treatable form of a confusional state. After 30 minutes (for generalized seizures) or 60 minutes (for focal seizures), if seizures continue despite the use of two antiepileptic drugs (AEDs), patients are considered to have refractory SE. Super-refractory SE (SRSE) is SE that persists despite 24-hour treatment with intravenous anesthetic agents and recurs when weaning patients off these agents**.** The causes of SE vary; they include stroke, infections, trauma and metabolic disorders. In children, fevers also are a causal factor **(22).**

Drug use is a factor for SE. It is estimated that 15% of patients with seizures secondary to drug use can develop SE, especially with the use of antibiotics. Particularly when used intravenously at high doses in patients with hepatic or renal dysfunction. It is noteworthy to mention that the antiepileptic drugs (AEDs) carbamazepine (CBZ), oxcarbazepine (OXC), and eslicarbazepine (ESL) may themselves represent a cause of hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion. Hyponatremia usually produces nonspecific electroencephalogram (EEG) slowing. A very severe hyponatremia may initially cause posterior slowing followed by diffuse delta activity **(23).**

Hypernatremia is defined as a serum sodium concentration in plasma >145 mEq/L**.** Hypernatremia is less likely to result in seizures and is more likely to be a consequence of seizures, particularly in generalized onset seizures due to osmotically active lactate driving water into cells. Hypocalcemia is defined as a plasma calcium level of <8.5 mg/ dL or an ionized calcium concentration <4.0 mg/dL**.** Hypocalcemia results in seizures, particularly with rapid changes in calcium levels and often requires rapid correction with IV calcium. Hypercalcemia is rarely associated with seizures due to decreased excitability of neuronal membranes **(24).**

Diagnosis of Epilepsy

The diagnosis of epilepsy is typically based on the description of the seizure and surrounding events. An electroencephalogram (EEG) and neuroimaging are also usually part of the workup. While figuring out a specific epileptic syndrome is often attempted, it is not always possible. Video-EEG monitoring may be useful in difficult cases. EEG continues to play a central role in diagnosis and management of patients with seizure disorders in conjunction with the new remarkable variety of other diagnostic techniques developed over the last years because it is a convenient and relatively inexpensive way to demonstrate the physiological manifestations of abnormal cortical excitability that underlie epilepsy **(25).**

Khalily et al., (26) stated that EEG may confirm diagnosis of true seizures. It helps classify seizure's type and diagnose epileptic syndromes. Also it can be used to assess prognosis and for follow up.

Inpatient video-EEG monitoring combines both a video and an EEG recording of clinical events. This test is used for diagnosis of true seizures and non-epileptic attacks (**27).**

In some series, more than 25 percent of individuals referred for monitoring for refractory epilepsy are found to have non-epileptic events, usually psychogenic non-epileptic seizures. EEG monitoring can also aid in seizure classification and is used for pre-surgical evaluation of epilepsy patients **(25).**

It is presently recognized that epilepsy can be associated with gross or subtle structural lesions of the brain. Modern neuroimaging is important in the diagnosis and treatment of patients with epilepsy especially for those patients who have medically intractable seizures. These neuroimaging modalities

include computed tomography (CT), magnetic resonance imaging (MRI), Positron emission tomography (PET), single photon emission tomography (SPECT), magnetic resonance spectroscopy (MRS) and functional magnetic resonance imaging **(28).**

Although the use of CT for patients with epilepsy has been greatly diminished by MRI, CT is still a helpful choice for the investigation of patients with seizures and epilepsy under certain conditions, for example it accurately detects hemorrhage, infarctions (after≥24h), gross malformations, ventricular system pathologies, and lesions with underlying calcification. CT has many advantages, like lower cost, scan speed, ready accessibility, and easy use, which provide a relatively reliable imaging modality for most patients **(29).**

By the time a patient is considered to have idiopathic epilepsy, study with MRI will usually have been performed. In many cases, this should be repeated, particularly if the original study was unrevealing. In some cases, follow-up MRI reveals an etiology for epilepsy (such as cerebral neoplasm, autoimmune encephalitis). The sensitivity of MRI for an underlying cause of epilepsy (so-called lesional epilepsy) can be substantially improved by using an epilepsy protocol; these are not routinely used outside of subspecialty epilepsy centers. Not all MRI findings are relevant. Isolated findings of diffuse atrophy, punctate foci of T2 signal abnormalities in the white matter and other nonspecific findings are not known to be epileptogenic. MRI findings should be correlated with the patient's seizure semiology and EEG findings. Some potentially epileptogenic lesions may be incidental (**30).**

Indications for MRI in patients with epilepsy are focal onset seizures, onset of generalized or unclassified seizures in the first year of life or in adulthood, focal deficit on neurological or neuropsychological examination, difficulty in obtaining seizure control with first line antiepileptic drugs (AEDs) and Loss of seizure control or change in the seizure pattern **(31).**

One of the most common and illustrative examples in which pathologic findings affect management in a patient with epilepsy is mesial temporal sclerosis (MTS). The presence of MTS in the context of temporal lobe epilepsy is a strong prognostic indicator for seizure intractability. Other symptomatic epilepsies may include those associated with tumors and malformations of cortical development **(30).**

Single photon emission CT (SPECT):

SPECT is not indicated for the majority of patients with epilepsy but it has an important role in the investigation of surgical candidates. The use of SPECT in epilepsy is based on the known association of seizures with increased ictal regional cerebral perfusion or interictal decreases in perfusion **(32).**

Positron Emission Tomography (PET):

Ictal PET studies of patients with partial seizures showed increase in regional cerebral glucose metabolism and blood flow in the region of epileptic focus**.** When a single region of metabolic abnormality corresponding to the EEG abnormality is detected, surgical treatment is effective in controlling seizures and improving developmental outcome **(31).**

Magnetic Resonance Spectroscopy (MRS):

In epilepsy, the abnormalities typically consist of reduced N-Acetylaspartate (NAA) signal and increased choline, creatine and myoinositol signals **(33).**

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