Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

An Updated General Overview of Seizures

Ahmed El Sayed Badawy, Aya Abd El Hakeem Younis, Mona Mohamad Amer
Department of Neurology, Zagazig University Hospital, Egypt.
Corresponding Author: Aya Abd El Hakeem Younis
Email: ayahbishr@gmail.com

Abstract

Background: Seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive synchronous neuronal activity in the brain, and epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. Epilepsy is diagnosed on having two unprovoked seizures occurring more than 24 hours apart, a single unprovoked seizure if recurrence risk is high (more than 60% over the next 10 years), or a diagnosis of an epilepsy syndrome is fulfilled. Acute Symptomatic seizures (ASS) are seizures closely temporally related to neurological or systemic insults, so that they are considered to be a symptom of an acute disorder affecting the brain either primarily or secondarily. The time window during which those acute seizures can be considered to be symptomatic for an acute disease is the period until clinical stabilization of that disease, and the International League Against Epilepsy (ILAE) suggested that it is the period of 1 week after stroke, head trauma, or anoxic encephalopathy; the active phase in CNS infection or inflammatory disease, based on persistent clinical, laboratorial, or imaging findings; within 24 hours of documented severe selected metabolic derangements; and within 7 to 48 hours of the last drink in alcohol withdrawal seizures.

Keywords: Seizures

Introduction

A seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive synchronous neuronal activity in the brain. A seizure is an event while epilepsy is a disease with recurrent spontaneously unprovoked seizures**.** Epilepsy is diagnosed when having two unprovoked seizures occurring more than 24 hours apart, a single unprovoked seizure if recurrence risk is high (more than 60% over the next 10 years), or a diagnosis of an epilepsy syndrome is fulfilled. Epilepsy is a disorder of the brain with an enduring tendency to induce epileptic seizures. It has neurobiological, cognitive and psychosocial effects on the individuals. The definition requires the occurrence of at least one unprovoked seizure with a high liability to develop additional seizures **(1).**

Globally, an estimated 2.4 million people are diagnosed with epilepsy each year. In high-income countries, annual new cases are between 30 and 50 per 100,000 people in the general population. In low-income and middle-income countries, this figure can be up to 2 times higher. This is likely due to the increased risk of endemic conditions, such as malaria or neurocysticercosis (NCC); the higher incidence of road traffic injuries and birth-related injuries; variations in medical infrastructure; and availability of preventive health programs and accessible care **(2).**

In low-income and middle-income countries, approximately 90% of patients live in resource-limited settings, according to the World Bank income classification **(3).**

It was frequently reported that the prevalence of epilepsy tends to be lower in developed countries (4.3–7.5/1,000) and remarkably higher in developing countries (17–57/1,000) **(4).**

Epilepsy is presumed to be one of the most common neurological disorders in Egypt with a median incidence rate in a study performed in Assiut governorate of 56.79 per 100,000 person per year **(5).**

Patients with epilepsy are at an increased risk of premature death with a mortality risk of 1.4 to 3.6 of all causes of death **(6).**

Pathophysiology of seizures

Pathophysiology of focal seizures:

The dysfunctional cerebral mechanisms of decreased inhibition, defective activation of gamma-aminobutyric acid (GABA) neurons, and increased activation may coexist in different combinations (hyperexcitability) causing focal-onset seizures. If any of these mechanisms becomes a permanent alteration, a propensity for recurrent seizures (i.e., epilepsy) presumably develops. Paroxysmal depolarization shift (PDS) in single cortical neurons is the cellular neurophysiologic correlate of the focal interictal epileptiform spike or sharp wave, which is the electroencephalographic (EEG) hallmark of focal-onset seizures. During PDS, a prolonged calcium-dependent depolarization results in multiple sodium-mediated action potentials during the depolarization phase, which is then followed by a prominent after-hyperpolarization phase, which is mostly mediated by calcium-dependent potassium channels. When multiple neurons (more than several

millions) fire PDSs in a synchronous manner (hypersynchronization), covering about 6 cm^2 of cerebral cortex, an interictal spike can be detected with scalp electrodes **(7).**

Pathophysiology of generalized seizures:

An altered thalamocortical interaction, disturbing the normal thalamocortical oscillatory rhythms, may result in primary generalized-onset seizures. This alteration is hypothesized to underlie typical absence seizures, which are considered to be the best example of generalized seizures. The pyramidal neurons of the neocortex, the thalamic relay neurons, and the neurons in the nucleus reticularis of the thalamus (NRT) form the thalamocortical circuitry, which normally has oscillatory rhythmsThe inhibitory NRT neurons (mainly GABA-containing) regulate the activation of the transient low-threshold calcium channel (T-calcium current) in thalamic relay neurons (GABA-B receptors-containing), leading to hyperpolarization which switches the T-calcium channels from the inactive state into the closed state, to be ready for activation when needed. This switching to the closed state permits the synchronous opening of a large population of the T-calcium channels every 100 milliseconds or so, generating the oscillations observed in sleep spindles in EEG.

It has been found in absence seizures animal models (lethargic mice) that GABA-B receptor antagonists suppress absence seizures, whereas GABA-B receptors agonists worsen them, and also AEDs that prevent absence seizures (as valproic acid and ethosuximide) suppress the T-calcium current, blocking its channels. **(8)**

Pathophysiology of convulsive seizures:

The spread of excitation to the subcortical, thalamic, and brainstem centers corresponds to the tonic phase of the seizure and to loss of consciousness as well as to the signs of autonomic nervous system overactivity (salivation, mydriasis, tachycardia, increased blood pressure) **(9).**

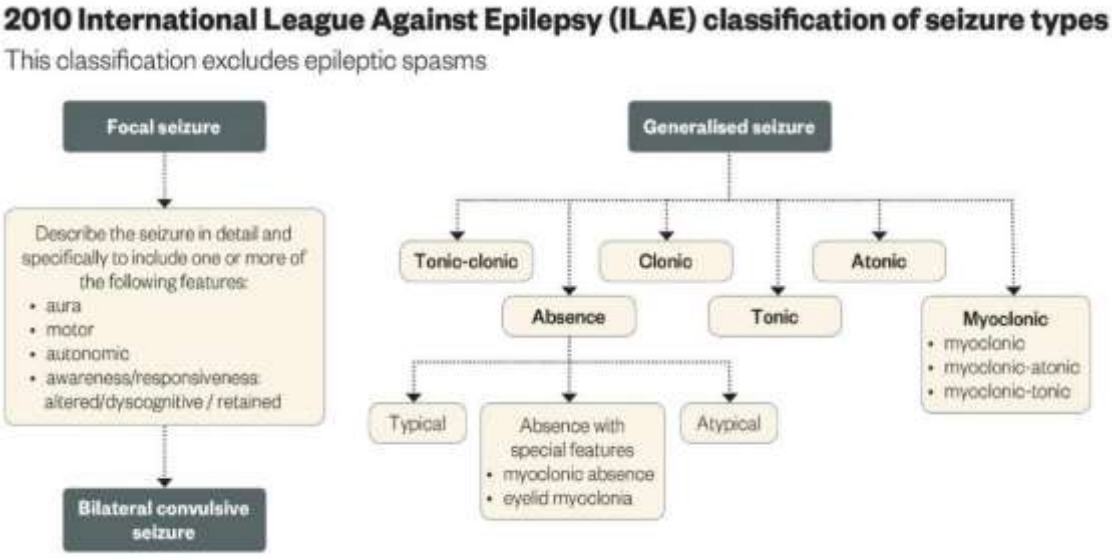
The development of unconsciousness and the generalized tonic seizures are reflected in the EEG by a diffuse high-voltage discharge pattern appearing simultaneously over the entire cortex **(10).**

Soon after the spread of excitation, a diencephalic inhibition begins and intermittently interrupts the seizure discharge, changing it from the persistent tonic phase to the intermittent bursts of the clonic phase. In the surface EEG, a transition occurs from a continuous polyspike to a spike and wave pattern. The intermittent clonic bursts finally cease, leaving an "exhaustion" (paralysis) of the neurons of the epileptogenic focus. An

excess of these inhibitory mechanisms and metabolic exhaustion are thought to be the basis of Todd's post epileptic paralysis and of postictal stupor, sensory loss, aphasia, hemianopia, headache, and diffuse slow waves in the EEG **(1).**

Classification of seizures:

The ILAE classification system for seizures and the epilepsies (2010) has formed the basis for a worldwide standardized approach to diagnosis, treating, and studying seizure disorder. The classification is based on clinical semiology and EEG correlation. New terminology for underlying causes (genetic, structural-metabolic, and unknown) was introduced to replace the old (idiopathic, symptomatic, and cryptogenic) in 2010. The use of generalized and focal to refer to the underlying epilepsy was largely abandoned, but the terms were retained in reference to mode of seizure initiation and presentation. The terms ''complex'' and ''simple partial'' for focal seizures were abandoned in favor of more descriptive terms **(11).**



ILAE seizure classification **(11).**

According to **Scheffer, I. E., et al, (12),** the new classification of the ILAE in 2017 continues to rely on semiology of seizure, EEG features and occasionally supplementary data from neuroimaging. Seizures are first categorized by type of onset. Focal-onset seizures are defined as originating within networks limited to one hemisphere. They may be localized or more widely distributed and may also originate in subcortical structures. Generalized onset seizures are defined as originating at rapidly engaging and bilaterally

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

distributed networks. Unknown onset is not a characteristic of the seizure but represents our lack of knowledge of the onset.

The phrase “focal to bilateral tonic–clonic” replaces the older term
“secondarely generalized tonic–clonic.” In the new classification, “bilateral” is used for propagation patterns of seizures and “generalized” for seizures of generalized onset. Generalized-onset seizures are divided into motor and nonmotor (absence) seizures. Level of awareness is not used as a classifier for generalized seizures, since the large majority (although not all) of generalized seizures are associated with impaired awareness.
Seizures of unknown onset can be categorized as motor, including tonic–clonic, nonmotor, or unclassified. The term unclassified comprises both seizures with patterns that do not fit into the other categories or seizures presenting insufficient information to allow categorization **(12).**

Focal motor onset behaviours include these activities: atonic (focal loss of tone), tonic (sustained focal stiffening), clonic (focal rhythmic jerking), myoclonic (irregular, brief focal jerking), or epileptic spasms (focal flexion or extension of arms and flexion of trunk). The distinction between clonic and myoclonic is somewhat arbitrary, but clonic seizure implies sustained, regularly spaced stereotypical jerks, whereas, myoclonus is less regular and in briefer runs. Other less obviously focal motor behaviours include hyperkinetic activity (pedaling, pelvic thrusting, jumping, thrashing and/or rocking movements), and automatisms. An automatism is a more or less coordinated, purposeless, repetitive motor activity **(1).**

Status Epilepticus (SE):

The definition of SE, as per the Neurocritical Care Society, defined as continuous or repetitive seizure activity lasting at least 30 minutes in duration without recovery of consciousness between attacks. The current and largely accepted operational definition is “at least 5 minutes of continuous seizures or discrete seizures with incomplete recovery of consciousness” **(13).**
The definition of SE per the ILAE is described as a condition resulting from either the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after 5 minutes) resulting in long-term consequences (after 30 minutes) **(14).**
Status epilepticus may be of the nonconvulsive type "nonconvulsive seizure" that may impair consciousness, but not manifested by any abnormal bodily movement. This represents an important and potentially treatable form of acute confusional state **(15).**

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

Diagnosis of seizures:

It is the clinician's first task to determine that an event has the characteristics of a seizure and not one of the many imitators of seizures; the next step is classification into a seizure type **(16)**.

Errors in diagnosis, seizure classification, and prognosis are known to lead to inappropriate decisions on the use or choice of antiepileptic drugs and to other serious patient management errors **(17).**

- **History and Physical examination:**

Patients presenting with a suspected first-time seizure should undergo an orderly evaluation

The first step is to distinguish the presenting episode from other paroxysmal events that can mimic seizures (see the table below), which can include migraine, transient ischemic attack, and syncope **(18).**

- The second step is to assess for provocative factors such as acute systemic disturbances or acute insults to the brain that would predispose a patient to acute symptomatic seizures.
- The history and clinical examination are the basis for evaluation of the first seizure, even in the era of neuroimaging and digital EEG recording **(19).**

The history should initially focus on **(20):**

- Determining whether a seizure actually occurred and evaluating the circumstances and characteristics of the event.
- The patient's experience, recollection, and awareness of the event. Subjective symptoms at the onset of a seizure are considered auras, which are typically seen in patients with focal seizures.
- Ask patients about prior events that may represent seizure symptoms. A large number of patients who experience a first convulsive seizure may also have had prior staring spells, or myoclonic jerks and would meet the criteria for the diagnosis of epilepsy or even a specific epilepsy syndrome.
- To evaluate and document patient and witness accounts separately. Doing so enhances the accuracy of the report.
- The first seizure evaluation should include an inquiry into signs suggestive of nocturnal seizures, such as waking in the morning to find a bitten tongue, blood on the pillow, urinary incontinence, or other unexplained injuries **(21).**

- A history of trauma or symptoms of infection (e.g., stiff neck, fever, headache), medication, illicit drug, and alcohol use also helps direct the evaluation.
- The patient should be asked about a history of neurologic or developmental disorders or a family history of epilepsy that will help to narrow the differential diagnosis **(22).**
    - ❖ General and neurological examination should be completed. The provider should look for signs of meningitis such as neck stiffness, photophobia, and Kernig's and Brudzinski's signs. Signs of increased intracranial pressure may be present, such as pupil dilation, sixth nerve palsy, or papilledema (particularly if subacute or chronic). Observation of forced gaze deviation, myoclonus, facial twitching, altered consciousness, loss of bowel or bladder control, and nystagmus may be related to ongoing seizure activity.

The occurrence of seizures can be suspected by clinical activity, but EEG confirmation is required. The clinical appearance of early seizures in the ICU includes generalized tonic-clonic and focal seizures. Complex partial seizures may also occur, but documentation of these in an intubated, sedated patient is difficult. Focal seizures can appear as rhythmic myoclonic activity or as a more subtle finding, such as a facial twitch **(23).**

- **Diagnostic Blood Testing:**

Metabolic screening for uremia, hypoglycemia, drug intoxications, and electrolyte disorders should be conducted for patients with first seizure who present to the emergency department.Toxicology screening should be performed when substance abuse is suspected **(24).**

- **EEG:**

A definite diagnosis usually requires capturing simultaneous clinical (video) and electroencephalographic seizures yet unfortunately this facility is only practical for patients with frequent ("intractable") seizures. Even with EEG recordings that capture seizures, some may be missed on surface EEG. Scalp electrodes cover only one third of the cortex, so discharges arising from buried cortex, such as amygdala, hippocampus, insula, and interhemispheric regions, may not be detected. A large area of the cortex (0.6

cm^2) must be firing to be detected on surface EEG. Although routine interictal EEG is an inexpensive and valuable tool, it still has its limitations. The sensitivity of the first EEG varies between 29% and 55% **(25).**

The misdiagnosis of epilepsy is often based on an "abnormal EEG" despite a history that is not particularly suggestive of epilepsy. This tendency to overemphasize the EEG to the detriment of the history is harmful. The history should be emphasized, not the EEG, unless very strong. Reasons for reading a normal EEG as abnormal include overreading normal variants such as wicket spikes, hypnagogic hypersynchrony, hyperventilation-induced slowing, fragmented alpha activity, or just simple fluctuations of sharply contoured background rhythms.The widespread misconception that a phase reversal is in itself abnormal, and indicative of seizures is unfortunately very common **(26).**

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 manifestations of abnormal cortical excitability that underlie epilepsy**.** Video-EEG monitoring may be useful in difficult cases **(National Clinical Guideline Centre (UK)., (27).**

There are few studies evaluating the best timeframe to increase the diagnostic yield of EEG after a first seizure. The periods considered "early" in the related studies are arbitrary and include the first 24 to 72 h after onset of the event. An article by the Italian League Against Epilepsy (LICE) showed level 3 evidence and level B recommendation for EEG to be performed within the first 24 h after new-onset seizure, especially in children Finally, EEG and other tests should not be overemphasized over the clinical picture and clinical judgment **(25).**

- **Neuroimaging:**

Neuroimaging in first non-febrile seizure evaluation identifies a structural brain lesion in 33% of adults, and in 50% of infants <6 months, so all adults should have neuroimaging after first seizure as per American College of Emergency Physicians (ACEP), and American Academy of Neurology (AAN), and it is typically a plain head CT (with contrast in HIV or cancer history), that needs to be followed later by a brain MRI, and the plan below is suggested **(28):**

Urgent neuroimaging indications in adults (typically a plain head CT):

1. Acute head trauma.
2. Age over 40 years.
3. AIDS.
4. Persistent altered mental status.

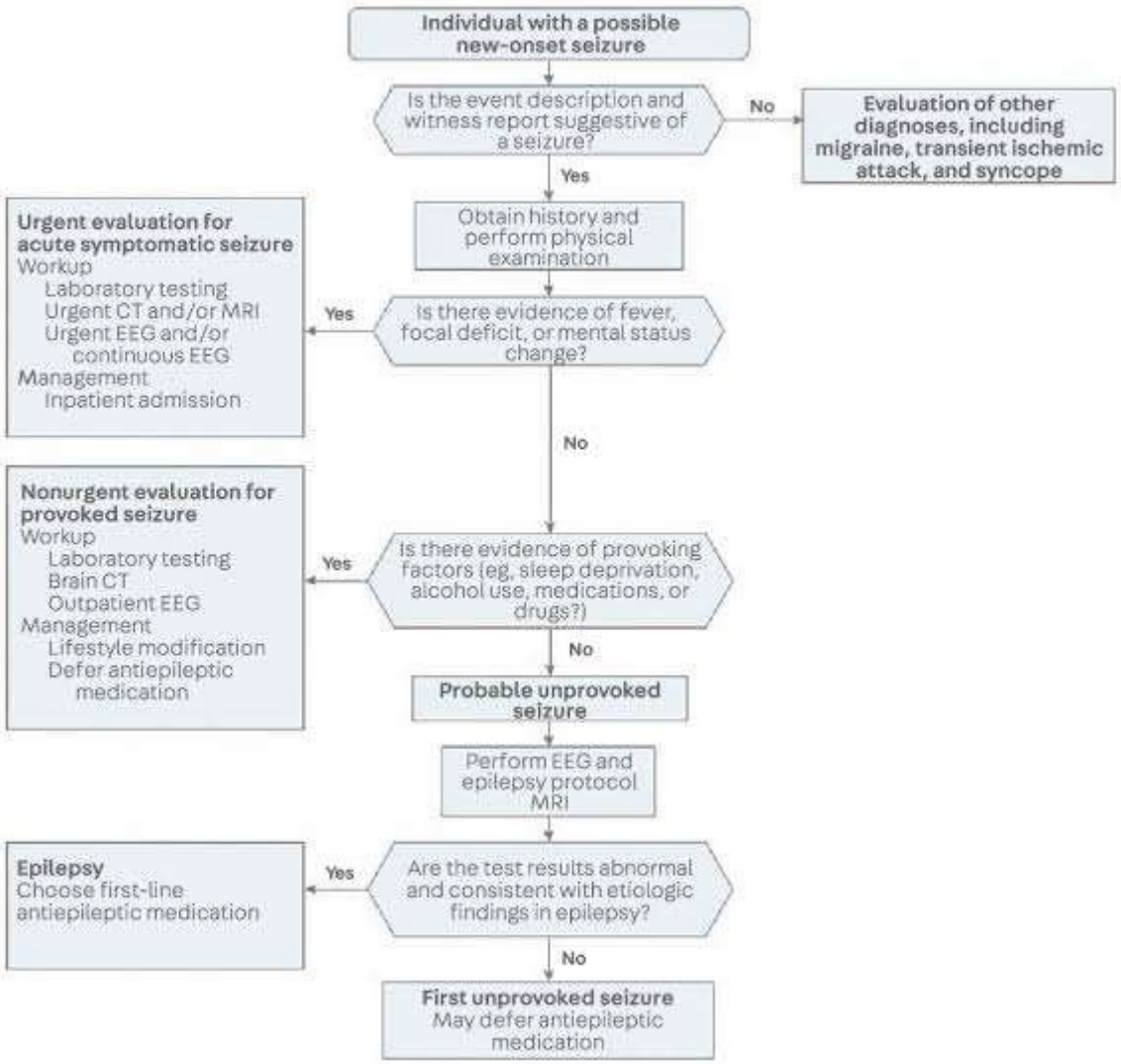
ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 07, 2021

5. Anticoagulation.
6. Fever.
7. Focal neurologic deficit of new onset.
8. Persistent headache.
9. Malignancy
10. Partial (focal) seizures.

Deferred outpatient neuroimaging indications in adults (typically a head MRI):

1. Stable patient.
2. No urgent neuroimaging indications.
3. Reliable patient for follow-up.
4. Return to baseline mental status during emergency department evaluation.

On the other hand, for patients with established diagnosis of epilepsy, they all should undergo an MRI, except those with very typical forms of primary generalized epilepsy (e.g., juvenile myoclonic epilepsy, childhood absence) or benign focal epilepsies of childhood with characteristic clinical and EEG features (e.g., benign epilepsy with centrotemporal spikes, early-onset childhood epilepsy with occipital spikes (Panayiotopoulos type)) and adequate response to antiepileptic drugs (AEDs) **(29**



Algorithm showing Systematic approach to a patient with a new onset seizure **(20).**

{CT: Computed Tomography, MRI: Magnetic resonance imaging, EEG: electroencephalogram}

References.

1. **Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., ... & Wiebe, S. (2014).** ILAE official report: a practical clinical definition of epilepsy. Epilepsia, 55(4), 475-482.

2. **Singh, A., & Trevick, S. (2016).** The epidemiology of global epilepsy. Neurologic clinics, 34(4), 837-847.

3. **Newton, C. R., & Garcia, H. H. (2012).** Epilepsy in poor regions of the world. The Lancet, 380(9848), 1193-1201.

4. **El-Tallawy, H. N., Farghaly, W. M., Rageh, T. A., Shehata, G. A., Metwally, N. A., Badry, R., ... & Tohamy, A. M. (2016).** Spectrum of epilepsy–prevalence, impact, and treatment gap: an epidemiological study from Al-Quseir, Egypt. Neuropsychiatric disease and treatment, 12, 1111.

5. **Khedr, E. M., Shawky, O. A., Ahmed, M. A., Elfetoh, N. A., Al Attar, G., Ali, A. M., ... & Farweez, H. (2013).** A community based epidemiological study of epilepsy in Assiut Governorate/Egypt. Epilepsy research, 103(2-3), 294-302.

6. **Thurman, D. J., Logroscino, G., Beghi, E., Hauser, W. A., Hesdorffer, D. C., Newton, C. R., ... & Epidemiology Commission of the International League Against Epilepsy. (2017).** The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia, 58(1), 17-26.

7. **Rho, J. M., Sankar, R., & Cavazos, J. E. (Eds.). (2004).** Epilepsy: scientific foundations of clinical practice. CRC Press.

8. **McCormick, D. A. (1992).** Cellular mechanisms underlying cholinergic and noradrenergic modulation of neuronal firing mode in the cat and guinea pig dorsal lateral geniculate nucleus. Journal of Neuroscience, 12(1), 278-289.

9. **Stafstrom, C. E. (2010).** Pathophysiological mechanisms of seizures and epilepsy: a primer. Epilepsy: mechanisms, models, and translational perspectives, 3-19.

10. Nir, Y., Massimini, M., Boly, M., & Tononi, G. (2013). Sleep and consciousness In Neuroimaging of consciousness (pp. 133–182).

11. **Berg, A. T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, J. H., van Emde Boas, W., ... & Scheffer, I. E. (2010).** Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009.

12. **Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., ... & Zuberi, S. M. (2017).** ILAE classification of the epilepsies:

position paper of the ILAE Commission for Classification and Terminology. Epilepsia, 58(4), 512-521.

13. **Meziane-Tani, A., Foreman, B., & Mizrahi, M. A. (2020, December).** Status Epilepticus: Work-Up and Management in Adults. In Seminars in Neurology (Vol. 40, No. 06, pp. 652-660). Thieme Medical Publishers, Inc.

14. **Moosavi, R., & Swisher, C. B. (2020, December).** Acute Provoked Seizures—Work-Up and Management in Adults. In Seminars in Neurology (Vol. 40, No. 06, pp. 595-605). Thieme Medical Publishers, Inc.

15. **Holtkamp, M., & Meierkord, H. (2011).** Nonconvulsive status epilepticus: a diagnostic and therapeutic challenge in the intensive care setting. Therapeutic advances in neurological disorders, 4(3), 169-181.

16. **Brodtkorb, E. (2013).** Common imitators of epilepsy. Acta neurologica scandinavica, 127, 5-10.

17. **Krumholz, A., Wiebe, S., Gronseth, G. S., Gloss, D. S., Sanchez, A. M., Kabir, A. A., ... & French, J. A. (2015).** Evidence-based guideline: management of an unprovoked first seizure in adults: report of the guideline development subcommittee of the American academy of neurology and the american epilepsy society: evidence-based guideline. Epilepsy currents, 15(3), 144-152.

18. **Cornes, S. B., & Shih, T. (2011).** Evaluation of the patient with spells. Continuum (Minneapolis, Minn.), 17(5 Neurologic Consultation in the Hospital), 984–1009.

19. **Nowacki, T. A., & Jirsch, J. D. (2017).** Evaluation of the first seizure patient: Key points in the history and physical examination. Seizure, 49, 54-63.

20. **Gavvala, J. R., & Schuele, S. U. (2016).** New-onset seizure in adults and adolescents: a review. Jama, 316(24), 2657-2668.

21. **Angus-Leppan H. (2014).** First seizures in adults. BMJ (Clinical research ed.), 348, g2470.

22. Adams, S. M., & Knowles, P. D. (2007). Evaluation of a first seizure. American family physician, 75(9), 1342-1347.

23. Korbakis, G., Vespa, P. M., & Beaumont, A. (2017). Traumatic Brain Injury and Critical Care Seizures. In Seizures in Critical Care (pp. 195-209). Humana Press, Cham.

24. Nass, R. D., Sassen, R., Elger, C. E., & Surges, R. (2017). The role of postictal laboratory blood analyses in the diagnosis and prognosis of seizures. Seizure, 47, 51-65.

25. Amin, U., & Benbadis, S. R. (2019). The role of EEG in the erroneous diagnosis of epilepsy. Journal of Clinical Neurophysiology, 36(4), 294-297.

26. Benbadis, S. R. (2013). "Just like EKGs!" Should EEGs undergo a confirmatory interpretation by a clinical neurophysiologist?. Neurology, 80(1 Supplement 1), S47-S51.

27. National Clinical Guideline Centre (UK). (2012). The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care. Royal College of Physicians (UK).

28. Dayan, P. S., Lillis, K., Bennett, J., Conners, G., Bailey, P., Callahan, J., ... & Kuppermann, N. (2015). Prevalence of and risk factors for intracranial abnormalities in unprovoked seizures. Pediatrics, 136(2), e351-e360.

29. Cendes, F., Theodore, W. H., Brinkmann, B. H., Sulc, V., & Cascino, G. D. (2016). Neuroimaging of epilepsy. Handbook of clinical neurology, 136, 985-1014.