



Headache among Patients with Epilepsy

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبَّحَانَكَ لَا إِلَهَ إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
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List of Abbreviations

Abb.	Full term
<i>AED</i>	<i>Antiepileptic Drug</i>
<i>CM</i>	<i>Chronic migraine</i>
<i>CN</i>	<i>Cranial nerves</i>
<i>CSD</i>	<i>Cortical Spreading Depression</i>
<i>CT</i>	<i>Computerized tomography</i>
<i>EEG</i>	<i>Electroencephalography</i>
<i>EM</i>	<i>Episodic migraine</i>
<i>ESR</i>	<i>Erythrocyte sedimentation rate</i>
<i>FAS</i>	<i>Focal aware seizures</i>
<i>FBTCS</i>	<i>Focal to bilateral tonic-clonic seizures</i>
<i>FDA</i>	<i>Food and Drug Administration</i>
<i>FHM</i>	<i>Familial Hemiplegic Migraine</i>
<i>FIAS</i>	<i>Focal impaired awareness seizures</i>
<i>fMRI</i>	<i>Functional Magnetic resonance imaging</i>
<i>GCS</i>	<i>Glasgow Coma Scale</i>
<i>GTC</i>	<i>Generalized tonic-clonic</i>
<i>ICHD-III</i>	<i>International Classification Headache Disorders-III</i>
<i>IHS</i>	<i>International Headache Society</i>
<i>ILAE</i>	<i>International League Against Epilepsy</i>
<i>IQR</i>	<i>Interquartile range</i>
<i>MRI</i>	<i>Magnetic resonance imaging</i>
<i>MWA</i>	<i>Migraine with aura</i>
<i>OSA</i>	<i>Obstructive sleep apnea</i>
<i>peri-IH</i>	<i>Peri-Ictal headache</i>
<i>PET</i>	<i>Positron emission tomography</i>
<i>post-IH</i>	<i>Post-Ictal headache</i>
<i>pre-IH</i>	<i>Pre-Ictal headache</i>
<i>PWE</i>	<i>Patients with epilepsy</i>
<i>TACs</i>	<i>Trigeminal Autonomic Cephalalgias</i>
<i>TIA</i>	<i>Transient ischaemic attack</i>
<i>TTH</i>	<i>Tension-type headache</i>

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INTRODUCTION

Epilepsy is the most common chronic brain disease and affects people of all ages. More than 50 million people worldwide have epilepsy; nearly 80% of them live in low- and middle-income countries (*WHO, 2019*).

The International League Against Epilepsy (ILAE) adopted a new practical definition for epilepsy as a disease with either recurrent unprovoked seizures (ie, two or more unprovoked seizures occurring at least 24 hours apart) or a heightened tendency toward recurrent unprovoked seizures (ie, a single seizure, accompanied by evidence from clinical, electro-encephalographic, or neuroimaging tests that a heightened risk [at least 60%] exists for future seizures over the next 10 years), or when an epilepsy syndrome is diagnosed (*Falco-Walter et al., 2018*).

Headache, especially migraine, is one of the most common comorbidities in epilepsy. The comorbidity of migraine may influence the choice of anti-epileptic medication (AED). Some AEDs such as topiramate and valproate have proven effective in migraine prophylaxis and are approved for this indication by the US Food and Drug Administration (FDA) (*Mameniškien et al., 2016*).

In 1906, Gowers first advanced the clinical hypothesis of a relationship between epilepsy and migraine, since the two

conditions show a well-recognized clinical, pathophysiological and therapeutic overlap (**Gowers, 1906**).

Recent studies, have been showed that 7% -57% of patients with epilepsy report active interictal headaches. Migraine is seen in 2% -26.3% of this population, while tension-type headache is seen in 9% -19.1%. Postictal headache is reported frequently in patients with epilepsy (PWE). These headaches generally have features of migraine (21% -53% of postictal headaches) (**Whealy et al., 2019**).

Headache frequently co-morbid with most chronic diseases such as epilepsy. For instance, a review conducted to see the relationship between headache and epilepsy reported the comorbidity of headache and epilepsy as a result of common genetic mutations and clinical features, but the suggested link is not revealed conclusive evidence of a real causal association. Further, studies also suggested that there are genetic relationships as well as common underlying pathophysiological mechanisms including the imbalance between excitatory and inhibitory neurotransmitters in epilepsy and headache, especially for migraine. Proposed theories for shared etiologies include ion channel dysfunction, glutamatergic mechanisms, and mitochondrial dysfunction. These suggest that the cause of headache and epilepsy are multifactorial and hence need different diagnostic and interventional approaches (**Duko et al., 2020**).

Interpretation of EEG can be important for the differential diagnosis of some disorders with headache as a presenting symptom. Interictal EEG (between headache attacks) is not significant in routine evaluation of these patients, but can be useful in patients with unusual symptoms suggesting epilepsy or migraine (*Miskov, 2008*).

The most definitely abnormal EEGs with unilateral or bilateral delta activity have been recorded during attacks of hemiplegic migraine, and during attacks of migraine with disturbed consciousness (*Sand, 1991*).

EEG abnormalities have been found in occipital, frontal, and temporal areas regardless of side of headache. Slow waves are the most common abnormality (52.64%) seen followed by sharp waves (42.10%) and spikes (5.26%) in descending order these abnormalities (slow wave, sharp wave and spike) are seen more in migraine with aura (MWA) and changes are more common in occipital region, followed by frontal region. Frontal EEG abnormalities are equally present in both types of migraine (*Hamad et al., 2014*).

According to the temporal relationship with seizures, peri-ictal headache (peri-IH) was divided into pre-ictal headache (pre-IH), ictal and post-ictal headache (post-IH) (*Mainieri et al., 2015*).

To make things even more difficult, new data suggest that a headache may sometimes be the only ictal manifestation of an epileptic seizure: so-called “ictal epileptic headache”. This entity has been cited in the defined and published classification of headache disorders (ICHD-III) (*Mameniškien et al., 2016*).

“Ictal epileptic headache” is headache caused by and occurring during a partial epileptic seizure, ipsilateral to the epileptic discharge, and remitting immediately or soon after the seizure has terminated. May be followed by other epileptic manifestations (motor, sensory or autonomic) (*IHS, 2018*).

“Post-ictal headache” is headache caused by and occurring within 3 hours after an epileptic seizure, and remitting spontaneously within 72 hours after seizure termination. Occurs in over 40% of patients with either temporal lobe epilepsy or frontal lobe epilepsy and in up to 60% of patients with occipital lobe epilepsy. It occurs more frequently after generalized tonic-clonic seizures than other seizure types (*IHS, 2018*).

Furthermore, headache is very common in the general population. Moreover, headache (especially migraine) is one of the most common comorbidities in epilepsy. So; this study participates in clarifying the relationship between headache and epilepsy which will improve the quality of epileptic patients and help in optimizing the therapeutic decisions of epileptic patients with headache.

AIM OF THE WORK

To estimate:

- Temporal relationship of headache (Pre-ictal, Ictal, Post-ictal) with respect to seizure
- Assess different types of Post-ictal headache (tension-type headache, migraine and cluster headache)
- Characteristics of EEG changes in epileptic patients with headache.

EPILEPSY

Seizure as a word, derives from the Greek meaning to take hold. Epileptic seizure is defined conceptually as: “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.” This definition was updated by the ILAE in 2005 (Fisher et al., 2005) and was not changed in 2014 when the definition of epilepsy was updated (Fisher et al., 2014).

In 2014, the International League against Epilepsy (ILAE) revised the definition of *epilepsy* as a disease of the brain with (1) at least two unprovoked (or reflex) seizures occurring greater than 24 hours apart, or (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, or (3) diagnosis of an epilepsy syndrome (Fisher et al., 2014).

Classification of seizures and epilepsies

The prior and current classification systems aim to group seizures according to clinical presentation and brain region onset and to group epilepsies according to seizure type, age of onset, probability of remission, EEG findings, radiologic findings, and genetics. The classification is important for communication and diagnostic purposes, but also for evaluating drug specificity and prescribing the most appropriate therapy.