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Migraine with Aura versus Seizure: Diagnosis and Treatment

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by

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Abstract

The purpose of this research and systematic literature review is to determine if obtaining an electroencephalogram (EEG) in patients presenting with migraine with aura would result in better and/or more prompt symptom management compared to empiric migraine treatment. In this review, the electronic databases; CINAHL, PubMed, Clinical Key, Cochrane Library and Dynamed Plus were used. Both keyword and mesh terms were used related to the pathophysiology of migraines and seizures along with guidelines for work-up and treatment of migraines and seizures. All articles chosen for review were published after 1999, except one. All articles were peer reviewed, and include randomized control trials (RCTs), systematic reviews, cohort, surveys, observational and meta-analyses. Articles were eliminated that were outside of the scope of the research question. For this review, 30 resources were selected. The research indicates strong correlation between migraine with aura and seizure activity, however there was not strong evidence for obtaining an EEG in every patient with migraine. The research suggests there are certain circumstances an EEG would be warranted in patients presenting with symptoms of migraine. In these circumstances a correct diagnosis would result in more prompt treatment. Insight was gained into symptomatic differentiation of the two conditions and therefore when an EEG may be helpful. Overall, more research is needed in the use of EEG specifically in migraine to ascertain how useful it would be.

Keywords: Migraines, seizures, epilepsy, electroencephalogram

Introduction

Migraines are a debilitating condition and a very common complaint in the primary care setting. Migraines not only interfere with productivity, but they also interfere with the quality of life of the person afflicted. Migraines and epilepsy are often co-morbid; a patient with one of the diagnoses is twice as likely to have the other diagnosis. As a primary care provider, it is imperative that we can recognize that abnormal brain electrical activity can produce symptoms similar to symptoms of migraine with aura. We must differentiate through history, physical exam, and appropriate diagnostic evaluation to provide the most efficacious treatment. Preventing delays in accurate diagnosis will improve the quality of life of the patient.

Statement of the Problem

There are many overlaps between the pathophysiology of migraines and seizure activity. A patient presenting with a migraine with aura in a primary care clinic will likely receive the empiric treatment which may result in many trials of medications to attempt to manage their symptoms. Aside from acute new onset, a significant work up is not typically completed for acute migraine. If a workup is completed it is typically imaging studies to rule out structural abnormalities. Electroencephalograms (EEG) are rarely ordered since seizure disorder is rarely in the differential diagnoses. Since there is an increased incidence in patients with migraine additionally having a seizure disorder it may be appropriate to include an EEG in the clinical work up of complaints of migraine with aura.

Research Question

In patients suffering from migraine with aura does obtaining an electroencephalogram (EEG) to ascertain possible underlying cause and most appropriate treatment compared to empiric migraine treatment result in better and/or more prompt symptom management?

Methods

A literature review was performed using electronic search databases; In this review, the electronic databases; CINAHL, PubMed, Clinical Key, Cochrane Library and Dynamed Plus were used. Both keyword and mesh terms were used to define a set of the literature discussing pathophysiology of migraines and seizures. Further literature searches were completed on guidelines for diagnostic studies and treatment of migraines and seizures. A variety of key terms were used when searching. Except for one article all other articles chosen for review were published after the year 1999, were peer reviewed, and included randomized control trials (RCTs), systematic reviews, cohort, surveys, observational and meta-analyses. Articles were eliminated that were outside of the scope of the research question. For this review, 30 resources were selected. Little research was found providing specific guidance on when to utilize electroencephalogram in migraine suffers, but much was found on the correlation between the two conditions.

Literature Review

Pathophysiology of Migraines, Seizures, and the overlap between them

The connection between migraines and seizures has been studied for many years. There are some investigators that deny a link between the two conditions while many more accept that there is a bidirectional link, in that individuals with epilepsy are more likely to have migraines, and individuals with migraines are more likely to have epilepsy. Clinically, both conditions can cause paroxysmal symptoms preceded by a visual aura. In fact, migraines associated with seizures are so common the most recent International Classification of Headache Disorders (ICHD-II) has expanded to include three additional categories; migraine-triggered seizures (5-

15% of patients with epilepsy), hemicrania epileptica (5% of patients with epilepsy), and postictal headaches (10-50% of patients with epilepsy) (Bianchin et al., 2010).

Although there are similarities between migraine with aura and seizure disorders there are notable differences. Migraines occur less often in childhood and elderly while epilepsy occurs more often in children and the elderly. Migraines occur more often in women whereas epilepsy is found equally between males and females. Migraine symptoms persist for longer with pain being the primary symptom. Seizures are relatively brief with additional symptoms of sensory, visual, and motor symptoms. The symptoms associated with the aura are different in each condition as well. In migraine the visual aura usually involves negative symptoms, slow spreading, and is monochromatic. In epilepsy aura is often shorter, more complex, brightly colored, and sometimes present with feelings of déjà-vu (Bianchin et al., 2010).

Evaluation of the pathophysiology of both conditions may give insight into the overlapping symptoms and treatments. Migraine aura is thought to be the result of cortical spreading depression. This is a wave of neuronal glial depolarization that moves slowly across the cerebral cortex (Papadakis & McPhee, 2020, p. 1005-1007). The depolarization is a loss of membrane potential, due to the excessive excitatory neurotransmitter glutamate, which results in a large current shift and release of vasoactive substances such as nitric oxide (NO) and arachidonic acid metabolites. This results in alteration in blood volume in the vessels; increase followed by decrease in blood volume (Qubty & Patniyot, 2020). Also, there is release of the vasoactive neuropeptide calcitonin gene-related peptide causes neurogenic inflammation, sensitization, and headache (Papadakis & McPhee, 2020 p.1005). Alteration in the trigeminal system that innervates cranial vessels and meninges appears to result in increased peripheral and central pain sensitization. Additionally, there appears to be brain changes as well as changes in

the functional connectivity of the brain in chronic migraine. Of note cortical spreading depression has also been seen following stroke, traumatic brain injury, and in seizures (Qubty & Patniyot, 2020).

Papadakis & McPhee (2020) state seizure activity is the result of paroxysmal abnormal neuronal discharges in the brain that leads to a temporary disruption of the cerebral function. Although seizure activity pathophysiology may seem more straightforward than migraine pathophysiology, it is multifactorial. Synchronous epileptic neuron discharges are the result of alteration in the sodium, potassium, and calcium channels. The depolarization may occur focally in the brain or may be generalized. Spread depends on the connectivity and local patterns of excitation and inhibition. It is believed that the inhibitory neurotransmitter GABA is involved in the termination of seizure activity. It also has been hypothesized that a dysfunction of GABA plays some role in seizure activity. Additionally, there are different etiologies of seizure activity including neuronal structural, metabolic abnormalities, brain malformations, ion channel dysfunction resulting from a single gene mutation in some idiopathic epilepsies, thalamocortical network dysfunctions seen in absence epilepsies and medial limbic network alterations seen in temporal lobe epilepsy. Status epilepticus and chronic epilepsy with recurrent seizures are associated with neuronal injury. These are thought to be reactive sclerotic changes in the hippocampus (Badawy et al., 2008, 2009).

In both migraine and epilepsy, depolarization and hyper-synchronization can occur through different pathways. Migraine is the result of hypo excitation and rebound hyperexcitation. In epilepsy paroxysmal hyperexcitation and change in cortical neuronal activity occurs (Cilliler et al., 2017).

In reviewing the literature there were several studies that evaluated the bidirectional link between epilepsy and migraines. One meta-analysis study completed a systematic review of 5 databases to determine the prevalence of migraine in individuals with epilepsy. Ten eligible studies with a total of 1,548,967 subjects were reviewed. There was a 52% increase in the prevalence of migraine found among individuals with epilepsy compared to those without epilepsy [PR: 1.52 (95% CI: 1.29, 1.79)]. There was also a 79% increase in the prevalence of epilepsy among individuals with migraines compared to those without migraine [PR: 1.79 (95% CI: 1.43, 2.25)]. Although confidence intervals were high, the greatest limitation of this analysis was that 6 of the 10 studies evaluated were based on unvalidated self-reporting questionnaires (Keezer et al., 2015).

Another study involving 597 patients from 32 epilepsy clinics evaluated the frequency and characteristics of migraine and seizure related headaches. They found that 12.4% of the group additionally experienced migraines. Of the 597 patients, 181 (30.3%) suffered prodromal, ictal, or postictal seizure related headaches (SRH). Authors compared patients that suffered from migraines and seizures to those that only had seizures. Individuals that suffered from migraines and seizures experienced postictal SRH more frequently (35.1% vs. 22.9%, $p = 0.022$) and these were more likely to be a migraine-type (61.5% vs. 30.8%, $p = 0.003$). These individuals also experienced prodromal SRH more frequently (10.8% vs. 3.4%; $p = 0.009$) and these more likely to be a migraine-type (75.0% vs. 33.3%, $p = 0.090$). The authors found that those with earlier onset of epilepsy had greater incidence of migraine. Those with a longer duration of epilepsy had greater risk of seizure related headaches. Researchers concluded migraine is an important co-morbid condition in epilepsy. Limitations of the study were that the information was based on questionnaires, and it had a relatively small number of participants (HELP Study Group, 2010).

A similar study evaluated 349 patients with known epilepsy to determine the types and frequency of headaches in this population. Nearly twenty seven percent of patients had migraines. Similarly, many (59.8%) of the migraines were suffered during the prodromal, ictal, or postictal periods. In this study females experienced migraine headaches more often than males (p=0.006). Individuals that experienced more than one seizure per month, but less than one seizure per week had more frequent migraines (p=0.017). The frequency of migraine-type headaches was significantly higher in patients receiving monotherapy (68.3%) compared to those receiving polytherapy (31.7%) (p=0.015). The author postulates that cortical spreading depression occurring after a migraine-type headache could reduce the threshold for an epileptic focus, which could increase the risk of seizures. Additionally, the author questions if the varying mechanisms of action in using different antiepileptic medications inhibits the cortical spreading depression which may explain the lower frequency of headaches in patients receiving polytherapy. The limitation of the study is that EEGs were not performed during the headaches, which as it relates to the research question, makes determining true migraine etiology difficult (Cilliler et al., 2017).

One cross-sectional cohort study evaluated 400 children with epilepsy to try to determine if children with a greater seizure burden or certain epilepsies had a higher risk of migraines. The prevalence of migraines among participants was 25%, which is greater than children without epilepsy (3% – 23%). Migraine was more prevalent in children ten years or older (p = 0.0009), children with benign epilepsy with centrotemporal spikes (p = 0.003), and children with juvenile myoclonic epilepsy (p = 0.008). Migraines were not more prevalent in those with intractable epilepsy. Only 50% of patients that experienced migraines one or more times per week had documented conversations with their neurologist about their headaches. The authors point out

that the cortical spreading depression in migraine and the epileptic discharges in epilepsy may affect one another. Seizure activity may lead to cortical spreading depression and/or activation of the trigemino-vascular system which could cause migraine. Like many other studies information was gathered from questionnaires, which could lead to reporting errors (Kelly et al., 2012).

Another cohort study looked at the definite, probably, and possible migraine prevalence in patients with Benign Rolandic epilepsy of childhood (AKA: childhood epilepsy with centrotemporal spikes) and cryptogenic/partial epilepsy. There were three cohorts with 53 participants in each cohort. There was similar prevalence of migraine in benign Rolandic epilepsy (37.7%) and in cryptogenic/partial epilepsy (35.8%) compared to the control (11%). Although this was a small study, the cryptogenic/partial epilepsy group experienced most of their migraines postictally compared to the benign Rolandic epilepsy group who did not. Benign Rolandic epilepsy occurs in childhood and typically does not continue past puberty. The authors do note that most of the children in the Benign Rolandic group were in the "active" phase during the study, and they could not predict if migraines would continue following cessation of seizures. This study is limiting in that it involves a very specific etiology of seizures versus a study that evaluated seizures of any/all etiologies (Wirrell & Hamiwka, 2006).

Authors of another study evaluated the potential pathophysiological link between the occurrence of migraine followed by the development of subclinical brain lesions. The study compared the prevalence of brain infarcts and white matter lesions in individuals with migraines to controls to identify migraine manifestations associated with the lesions, using MRI. There were 435 participants ages 30-60. The researchers found no significant difference between patients with migraine and controls in overall infarct prevalence (8.1% vs 5.0%). In the cerebellar region of the posterior circulation territory, patients with migraine had a higher

prevalence of infarct than controls (5.4% vs 0.7%; P =.02; adjusted Odds Ratio (OR), 7.1; 95% CI, 0.9-55). In migraine with aura the adjusted OR was 13.7 (95% CI, 1.7-112) compared with controls. The highest risk for lesion was found in patients with migraine with aura with one attack or more per month (OR, 15.8; 95% CI, 1.8-140). Researchers concluded that some individuals with migraines are at risk for subclinical brain lesions. The limitations of this study are that the sample size was small and there is no real discussion of cause and effect; did the lesion cause the migraine or the migraine cause the lesion. If migraines contribute to lesions, studying an older population with a long history of migraines may have elicited more information (Kruit et al, 2004).

Most studies evaluated migraines in individuals with seizures, but migraines prior to seizures have not been widely studied. A case control study was completed to evaluate if migraine is a risk factor for epilepsy. Medical records of 140 participants with a history of unprovoked seizures under the age of sixteen were evaluated for a history of migraines. Migraine was found in 20.2% of individuals with seizure disorder and 6.9% in controls. The study found that that migraine with aura (determined as migraine with visual symptoms of zigzag lines, heat waves, blurry vision, or loss of vision) was associated with an average of 3.7-fold increased risk for developing epilepsy (odds ratio, 8.1; 95% confidence interval, 2.7–24.3). Migraine without aura did not increase risk for epilepsy. There was also greater risk for females, for partial compared to generalized seizures, and for those with epilepsy compared to those with single unprovoked seizures. There was also a noted increased prevalence of epilepsy seen with increasing age. The authors stress the importance of identifying which condition occurred first. Again, this was a small study, so definitive conclusions cannot be made (Ludvigsson et al., 2006).

Genetic similarities may play a role in explaining the comorbidity of migraines and epilepsy. Winawer & Connors (2013) investigated the potential shared genetics between migraine and epilepsy through the Epilepsy Phenome/Genome Project. Information on migraine occurrence was collected from 730 participants from 501 families with a history of 2 or more unprovoked seizures or 1 seizure with epileptiform electroencephalography (EEG). The results showed what appears to be ~30% (CI 95%) increase in migraine with aura in individuals who have 2 or more first degree relatives with a history of epilepsy. There was no increase of migraine without aura found. This suggest that there is some shared genetics between migraine with aura and epilepsy. One limitation identified is that there was health history information used to make some conclusions was based on participants report of non-enrolled relatives. This limitation seemed outweighed by the study using detailed medical records, diagnostic interviews, imaging, and EEG data.

Typical/ Empiric Treatment for Migraines

Empiric treatment of migraines primarily involves avoiding migraine triggers and symptomatic therapy to be taken at migraine onset. Pharmacologic interventions at migraine onset include simple analgesics (ibuprofen, acetaminophen, aspirin, naproxen) and abortive prescription medications include ergotamines and serotonin agonists (triptans). Medication overuse headaches can be avoided by using acute treatments less than fifteen days per month and combination medications less than ten days per month. Prophylactic medication should be recommended for patients who have two to three migraines per month or who have debilitating migraines. Medications used for prophylaxis include anticonvulsant medications (topiramate, valproic acid and gabapentin), antihypertensives (candesartan, guanfacine, propranolol and verapamil), antidepressants (amitriptyline, venlafaxine), monoclonal antibodies (erenumab,

fremanezumab, galcanezumab), additionally botulism toxin A and riboflavin has been used (Papadakis, M. & McPhee, S., 2020).

Triptans (5-HT1B/1D receptor agonists) are often prescribed initially for acute migraine when over the counter analgesics do not adequately manage migraine pain. They work through selective trigeminovascular neuronal inhibition. A randomized control trial assessed the effectiveness of treatment. One hundred fifty-eight patients between the ages of 18 and 65 years, with or without aura with one to eight migraine attacks a month were recruited. The study found that doses of 60 mg and 200 mg were effective with a 2-hour response 31-52%, 2-hour sustained response 23-34%, 2-hour pain free rates 29-44%, and 2-hour sustained pain free rates of 19-29%. The most common adverse effects were asthenia, dizziness, somnolence, and paresthesia with greater incidence with increased dose. Overall, the study found that triptans are effective in acute migraine management. This is a relatively small study, but there are numerous studies, not included in this review, with the same conclusion, hence standard treatment of acute migraine includes triptans (Goldstein et al., 2001).

Regarding prophylactic treatment of migraines one study completed a thorough review of 284 abstracts between 1999 and 2009 to provide updated evidence-based recommendations for the prophylactic treatment of migraines. Class I, level A recommendation was given to divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, and timolol to reduce migraine frequency. Frovatriptan is recommended for prevention of menstrual migraine. Lamotrigine is not effective for migraine prevention. This study was again consistent with practice guidelines for migraine prophylaxis. Although the overall number of study participants was not listed, a benefit of this study is that it looked at 284 different studies regarding migraine prophylaxis. Unfortunately, the authors point out that there is insufficient evidence that would

assist a provider in choosing the best medication class for a particular patient. There remains the trial-and-error approach where a provider and patient must determine the best treatment option based on adverse reactions, comorbid conditions, and other personal factors. Also, the study could not determine which medication within an individual class would be the most efficacious (Silberstein et al., 2012).

A review article looked a little further into anti-epileptic medications specifically for the treatment of migraines. These mediations have the potential to block cortical spreading depression and prevent central sensitization seen in migraines and seizure activity. They are thought to act by stabilizing neuronal membranes through their effect on voltage and receptor-gated ion channels and reducing the release of vasoactive neuropeptides. Topiramate specifically works on the NMDA (glutamate) receptor to decrease excitement. Topiramate, particularly long acting, is recommended as a first option in migraine prophylaxis. The authors found evidence that the use of topiramate significantly improved mean functional disability scores compared to amitriptyline. A combination of topiramate and amitriptyline had better efficacy than either alone. Evidence suggests that valproic acid would be a good second choice to topiramate. The authors cite an analysis that suggests those taking valproic acid had a >50% decrease in headache frequency compared to placebo. Additionally, they found that for migraine prevention valproic acid was as effective as propranolol, but slightly less effective than topiramate. Although this paper was a review rather than original research it did provide more definitive guidelines in migraine prophylaxis treatment (Parikh & Silberstein, 2019).

Effects of Delayed Treatment

Migraine is a debilitating condition that not only impacts the individual but also impacts many aspects of the family and society. A 2016 Global Burden of Disease study reveals that

migraine ranks second only to low back pain in years lost due to disability, which is 5.6% of all productive years lost due to disability globally. Migraine is the leading cause of years lost due to disability in peak productive years in ages 15 to 49. The authors outline that there are negative impacts to school, relationships, family planning, mental health, and career trajectory. In the United States the direct cost of migraine is greater than 28 billion dollars. The health cost burden for an individual with migraines compared with a matched control individual is 9,000 dollars more per year (Qubty & Patniyot, 2020).

One study assessed 520 individuals with chronic and 9,424 with episodic migraine using a validated questionnaires for the diagnosis of episodic and chronic migraine. Over a three-month period, more than 50% of the individuals with chronic migraine missed at least five days of household work, compared with 24.3% of those with episodic migraine ($p < 0.001$). Over the same period there was reduced productivity in household work in 58.1% with chronic migraine and 18.2% with episodic migraine ($p < 0.001$) for at least five days over three months. There was at least five days of missed family activities was reported by 36.9% with chronic migraine and 9.5% with episodic migraine ($p < 0.001$). Eighty seven percent of individuals with chronic migraine had previously sought care to discuss their headaches with a health care professional. The questionnaires also asked participants to report the medications currently used for their most severe headaches and provide the level of satisfaction with the treatment. Migraine-specific acute treatments were used by 31.6% individuals with chronic migraines and 24.8% with episodic migraine. Around 48% of the individuals with chronic migraines were satisfied with their acute therapies. Thirty-three percent of those with chronic migraines were currently using preventive medications. Despite chronic migraines being more disabling than episodic migraines, and 52% of individuals unsatisfied with their acute migraine treatment, only one-third of individuals with

chronic migraines were using prophylactic medication. A limitation of a questionnaire-based study is that the information gathered is subjective, without an ability to standardize data and answers. The information is also based on an individuals' recollections, which is not always accurate. The study did not elicit information on other factors that may have impacted the individual's current treatment with acute and prophylactic medications i.e., insurance coverage, desire to take medication etc. Overall, the information gathered from the study indicates that migraines, either chronic or episodic, do significantly interfere with quality of life and productivity of individuals that suffer from them (Bigal et al., 2008).

A Chronic Migraine Epidemiology and Outcomes (CaMEO) Study, a longitudinal web-based panel, assessed patterns and barriers to medical care. Barriers include accessing medical consultation, obtaining accurate diagnosis, and receiving pharmacological treatment. One thousand two hundred fifty-four participants with chronic migraine were included in the study. Five hundred twelve individuals (40.8%) reported currently consulting with a healthcare professional for chronic migraine. The rate of consultation increased with increasing age (95% CI 1.01-1.03), body mass index (BMI) (95% CI 1.00-1.03), migraine-related disability (95% CI 1.00-1.04), migraine severity (95% CI 1.11-1.22) and the presence of health insurance (95% CI 3.05-6.96). Of the 512 individuals who sought care 126 (24.6%) received an accurate diagnosis. Fifty-six individuals (44.4%) who received an accurate diagnosis received both acute and preventive pharmacologic medications. Chronic migraine was more often diagnosed in women (95% CI 1.03-3.61), those with greater migraine severity (95% CI 1.14-1.37), and those currently consulting a specialist (95% CI 1.54-3.69). There was no prediction regarding medication efficacy. Only 56 individuals (4.5%) in the study were able to complete all three barriers to migraine management. This study was completed in 2016 and should remain applicable today.

The level of the confidence intervals indicates some consistent trends in seeking care for migraine relief; greater age, greater severity/disability, obesity, and health coverage. This study did have a moderate number of participants, but again was based on data provided by individuals and self-reporting, which may not always be accurate (Dodick et al., 2016).

Despite the current recommendations for offering prophylactic treatment, one study reveals that more than one fourth of patients with migraines are candidates for prophylaxis and would benefit from it, but do not receive it. Researchers mailed 120,000 validated self-administered headache questionnaires using The International Classification of Headache Disorders criteria to determine migraine sufferers. Prevalence of migraine peaked in middle life and was lower in adolescents and those older than age 60 years. Thirty-one percent had migraine frequency of three or more per month, and 53.7% reported severe impairment or the need for bed rest. In 38.8% prophylaxis should have been offered or considered. Only 13.0% reported current use of daily preventive migraine medication. Unfortunately, the study does not reveal if these individuals were offered prophylactic treatment, and just declined. There was an increase in migraine prevalence as income decreased so insurance coverage and inability to seek care may have been contributing factors (Lipton et al., 2007).

In looking into the consistency in which seizure disorders/epilepsy are diagnosed and treated, one study evaluated the gap in new onset epilepsy and treatment. Researchers found that one-third of individuals diagnosed with epilepsy were untreated three years post diagnosis. The primary study consistent of 59,970 individuals that met the inclusion criteria for epilepsy and 36.7% with newly diagnosed epilepsy remained untreated up to three years after diagnosis. In the validation study (N = 30,890), 31.8% of individuals with epilepsy remained untreated up to three years after diagnosis. The authors additionally evaluated the health outcomes in treated versus

untreated cohorts. They found a 20% increased risk of any medical event in untreated individuals with epilepsy, ranging from falls or fractures (20%) to suicidality (70%). There was also greater than two-fold increased risk of hospitalizations and ED visits in untreated individuals. Lacking treatment with antiepileptic medications resulted in increased rates of medical events, hospitalizations, and emergency department visits (CI 95%). This study had many participants and used data from electronic medical records searching for ICD-9 codes and associated prescriptions, and therefore was based on providers making a diagnosis and prescribing a medication. The authors note that there could be an even greater gap in untreated patients as they do not know if the prescriptions were filled by the patient. A limitation of the study was that the authors did not have information regarding the decision-making process of the patients and providers. The authors discuss that providers may have approached treatment more conservatively based on several factors, or perhaps patients declined treatment (Kalilani et al., 2019).

Diagnostic work up and findings

The diagnosis of migraine is typically a clinical diagnosis, with no work-up indicated. The International Headache Guidelines defines migraine with aura as at least two attacks with one or more reversible symptoms of aura (visual, sensory, speech and/or language, motor, brainstem or retinal) or at least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache.

In one study, interviews and a brief questionnaire were given to 83 primary care providers in that hospital network to assess their knowledge in migraine diagnosis and treatment. It revealed that migraines are often under-recognized, misdiagnosed and inadequately treated in the primary care setting. The providers were aware of the prevalence of migraines but did not have a consistent understanding of diagnosis and management. Forty-seven percent of providers would order imaging for a new type of headache, 31% for worsening headache, and 35% for a headache unresponsive to treatment. Only 28% were familiar with the American Academy of Neurology guidelines on preventive treatment and 40% were familiar with the Choosing Wisely Campaign recommendations on migraine treatment. Only 34% were aware that opioids can cause medication-overuse headache. This study was limited by a very small number of providers questioned in just one hospital network (Minen, 2016).

A study conducted by a Headache Center looked at the relationship between the time of symptom onset and time of correct diagnosis. In 180 consecutive patients that went to the center and were given their first diagnosis of migraine, 16.7% were diagnosed in less than one year and 40% saw at least one specialist. Eighty three percent were diagnosed in more than one year and 38.9% saw at least one specialist. Fifty three percent were diagnosed in five or more years and 56.25% saw at least one specialist. Optometrists/ophthalmologists were the specialty most often referred to at 25.5%. Radiologic and laboratory exams increased as the time to diagnosis increased; 70% of patients performed one or more radiologic exams. Again, this was a small sampling of individuals, it is unclear if the information gathered was based on the medical record or patient report. Additionally, information was gathered from one Headache Center (Viticchi et al., 2010).

Although lengthy testing can delay diagnosis and increase costs, an electroencephalogram (EEG) would be the preferred test to rule in or rule out abnormal brain electrical activity as the source of migraine with aura symptoms. EEG changes can often be seen in subclinical epilepsies whereas in migraines there is a lack of habituation (Bianchin et al., 2010).

In looking at a systematic-prospective study of occipital seizures with elementary visual hallucinations, EEG was helpful in making a specific diagnosis. In the 1,360 participants that had been previously diagnosed with epilepsies, 4.6% had occipital seizures, 25.4% probable/definite non-photosensitive idiopathic occipital epilepsy with visual hallucinations, 38.1% early onset benign childhood occipital seizures, 27% symptomatic occipital epilepsy, and 9.5% idiopathic photosensitive occipital epilepsy. The authors' aim was to distinguish the differences in visual aura in migraine from that of occipital epilepsies. The study also revealed that all but two patients were initially misdiagnosed with migraine with aura, acephalgic migraine or basilar migraine and proper treatment was delayed. The study determined that visual hallucinations associated with epilepsies are typically colored and small circular flashing in a temporal hemifield. These visual hallucinations last for seconds but occur frequently, develop fast and have the same progression each time. Additional symptoms may include eye and head deviation, illusions of eye movement, eyelid repetitive closures, or fluttering. Postictal headaches are common and cannot be differentiated from migraine. The visual aura of migraine presents with linear, zigzag, and achromatic or black. Onset is gradual over minutes and exists towards the periphery of one hemifield and often leaves a partial alteration in the field of vision (scatoma) and rarely occurs daily. Although there was a relatively large sample size for one study, this

study was very focused on seizure diagnosis with EEG versus distinguishing seizure from migraine with aura using EEG (Panayiotopoulos, 1999).

In evaluating the relationship between migraine and epilepsy one study interviewed 395 adult seizure patients. Seventy-nine patients (20%) also had migraine syndrome, and 13 of these patients (3%) experienced seizures during or immediately following a migraine aura. Patients with catamenial epilepsy (epilepsy associated with menstrual cycle) and patients with migraine with aura were at an increased risk for comorbidities. Interestingly, in two patients the researchers obtained EEG for the duration of a migraine aura that progressed to partial seizure. There were distinctive changes on the EEG during the migraine aura that preceded the onset of an electrographic complex partial seizure. Periodic lateralized epileptiform discharges were recorded in five other patients in close temporal relation to their migraine attacks. It was found that there was improved seizure control with combination antimigraine and antiepileptic drugs in six patients who failed to respond to antiepileptic drugs alone. Unfortunately, in this case obtaining an EEG only improved treatment outcome in 1.5% of participants (Marks & Ehrenberg, 1993).

In pursuit of finding research regarding the value of EEG in the diagnosis of conditions outside of what they are typically utilize for, a study was completed that used EEG for evaluation of patients that experienced a paroxysmal state. EEG was used in the evaluation of inpatients after patients experienced one of the following: a solitary unprovoked epileptic seizure, sporadic epileptic seizures, "chronic" epilepsy, outpatients with epilepsy, syncope, neurocardiogenic syncope, migraine, and tetanic syndrome. Epileptic EEG changes were registered in 14.29% of the 84 patients after solitary unprovoked epileptic seizures, 25.7% of the 179 patients with sporadic epileptic seizures, 37.34% of the 324 patients with chronic epilepsy and 32% of the 300

outpatients with epilepsy. Interictal EEG abnormalities were found in 5% of the 100 patients with migraine, 4% of the 100 patients with tetanic syndrome and 2% of the 70 patients with syncope. The author points out that EEG is a non-invasive tool that can be used as one component of making a diagnosis. Again, in looking at EEG use in migraines only 5% had abnormal EEG findings, but the study did not indicate if these were migraines with or without aura (Kollar et al. 2014). A similar yet smaller study evaluated EEGs in 95 patients with transient neurological deficit in the preceding seven days with a median 1.6-day delay after symptom onset. Three groups were established. Thirty patients were in the "ischemic" group, 13 patients were in "migraine aura" group, 18 patients were in the "focal seizure" group, and 34 patients were categorized as "other." Forty EEGs (42%) were abnormal. Focal slow waves were the most common finding (43%). Epileptiform discharges were found in three patients, one with focal seizure and two with migraine with aura. In migraine with aura this represents 15% ($p=0.03$) of the patients examined. The 1.6-day delay in obtaining and EEG following symptoms may have impacted the study results (Lozeron et al., 2018).

In evaluating EEG in patients with migraines a small study evaluated the EEG of nine pediatric patients during a migraine and seven days post migraine. During migraine the EEG showed excess focal slowing in the delta or theta range localized on the parietal-occipital or temporal regions in seven patients with migraine with aura and in two patients with basilar migraine. All participants had EEG changes during their migraine. Post migraine EEGs were unremarkable. This study is limited by the very small number of participants and that it was only in the pediatric population (Pisani & Fusco, 2004). There was a similar finding in a slightly larger study that evaluated 41 participants with migraine using EEG and visual evoked potentials 36 hours prior to a migraine and 72 hours after a migraine. Frontocentral, temporal and

occipitoparietal hemispheric slowing and asymmetry was seen appeared within thirty-six hours of migraine onset with increased power. Following the migraine power and power asymmetry were not significantly different from baseline. EEG activity seems to change shortly before the attack. In this study 33 of the 41 participants experienced migraine without aura and only eight had migraine with aura, therefore this study was not especially informing to the research question (Bjork et al., 2011).

Brinciotti et al. (2000) looked at both the clinical and EEG differences between migraines and occipital epilepsy. This study involved 126 children with occipital epileptiform abnormalities on their EEG at rest. Sixty-three were suffering from epilepsy, 43 from migraine and 20 with both. The findings revealed characteristics in the epilepsy group included a family history of epilepsy, visual symptoms such as with colored hallucinations and micro/macropsias (50%), unilateral EEG abnormalities (43%), and abnormal response to photic stimulation (68%) and clinically were associated with clinical signs in the visual system such as eye deviation and nystagmus (35%). Characteristics found in the migraine group include a family history of migraine, visual symptoms such as partial or total blindness (amaurosis) and scotomata (35%), bilateral EEG abnormalities (95%) with no changes with photic stimulation and without evident clinical signs. Again, this study only involved a pediatric population.

Discussion

Although there are no large studies that have specifically evaluated the research question posed, the summation of many studies provides some cumulative data. Insight was gained into several areas regarding the pathophysiologic overlap of migraines and seizures as well as differentiation and treatment of the two conditions.

The first question that must be evaluated: Is there a physiologic overlap of migraines and seizure activity? Clinically, both conditions can cause paroxysmal symptoms preceded by a visual aura (Bianchin, et al., 2010). Authors agree that migraine with aura is likely the result of cortical spreading depression (Papadakis & McPhee, 2020, p. 1005-1007). Qubty, W., & Patniyot, I. (2020) state that cortical spreading depression has additionally been observed in conditions such as stroke, traumatic brain injury, and seizures. Papadakis & McPhee (2020) define seizure activity as the result of paroxysmal abnormal neuronal discharge in the brain that leads to a temporary disruption of the cerebral function. Causes of changes in hyperexcitability in the epileptic brain range from abnormalities of neuronal structure and organization in cortical malformations, abnormalities in neuronal metabolism in mitochondrial disorders, single gene mutations resulting in ion channel dysfunction in some idiopathic epilepsies, and disturbances in network function such as in the thalamocortical network in absence epilepsies and the medial limbic network in temporal lobe epilepsy (Badawy et al., 2008,2009). In both migraine and epilepsy, depolarization and hyper-synchronization can occur through different pathways. Migraine is the result of hypo excitation and rebound hyperexcitation occurs. In epilepsy paroxysmal hyperexcitation and change in cortical neuronal activity occurs (Cilliler et al., 2017). Several authors report that the cortical spreading depression in migraine and the epileptic discharges in epilepsy may affect one another. Seizure activity may lead to cortical spreading depression and/or activation of the trigemino-vascular system which could cause migraine (Kelly et al., 2012). Also, cortical spreading depression occurring after a migraine-type headache could reduce the threshold for an epileptic focus, which could increase the risk of seizures (Cilliler et al., 2017).

One author states status epilepticus and chronic epilepsy with recurrent seizures are associated with neuronal injury and reactive sclerotic changes in the hippocampus (Badawy et al., 2008, 2009). Similarly, Kruit et al. (2004) found patients with migraines had a higher prevalence of infarct in the cerebellar region of the posterior circulation territory than controls (5.4% vs 0.7%; P =.02; adjusted Odds Ratio (OR), 7.1; 95% CI, 0.9-55). The highest risk for lesion was found in patients with migraine with aura with one attack or more per month (OR, 15.8; 95% CI, 1.8-140). Researchers concluded that some individuals with migraines are at risk for subclinical brain lesions. The question becomes does the migraine cause the lesion, or does the lesion cause the migraines? If it is the latter, as mentioned brain lesions are known to cause abnormal brain electrical activity. Ludvigsson et al. (2006) notes an increased prevalence of epilepsy seen with increasing age, which may aid to the hypothesis of subclinical brain lesions associated with chronic migraines contributing to epilepsy later in life.

Badawy et al. (2008, 2009) point out that there are known genetic epilepsies. There also appears to be genetic links in migraines, as well as a genetic connection between migraines and epilepsies. The Epilepsy Phenome/Genome Project showed ~30% (CI 95%) increase in migraine with aura in individuals who have two or more first degree relatives with a history of epilepsy, suggesting shared genetics between migraine with aura and epilepsy (Winawer & Connors, 2013).

Several studies have reinforced the idea of a bidirectional link between epilepsy and migraine. Keezer et al. (2015) found an overall 52% increase in the prevalence of migraine among people with epilepsy versus those without epilepsy [PR: 1.52 (95% CI: 1.29, 1.79)]. There was an overall 79% increase in the prevalence of epilepsy among migraineurs versus those without migraine [PR: 1.79 (95% CI: 1.43, 2.25)]. Ludvigsson et al. (2006) evaluated medical

records to determine if patients complained of migraines prior to the development of epilepsy and found migraines in 20.2% of individuals with seizure disorder and 6.9% in controls. Migraine with aura was associated with an average of 3.7-fold increased risk for developing epilepsy (odds ratio, 8.1; 95% confidence interval, 2.7–24.3). Again, this makes a sturdy connection that migraine with aura may be the result of abnormal brain electrical activity in some cases, with between 20%-79% of individuals with migraines developing epilepsies. Several studies had corroborating data regarding the bidirectionality of the two conditions. Information from epilepsy clinics revealed 12.4% of the group had migraines. Individuals that suffered from migraines and seizures experienced postictal SRH more frequently (35.1% vs. 22.9%, $p = 0.022$) and these were more likely to be a migraine-type (61.5% vs. 30.8%, $p = 0.003$). Postictal migraines were the most common (35.1%) and 61.5 % were more likely to experience migraine type symptoms (HELP Study Group, 2010). Similarly, Cilliler et al. (2012) in their study population of known epilepsy found that 26.9% of those individuals additionally suffered from migraines. Again, many (59.8%) of the migraines were suffered during the prodromal, ictal, or postictal periods. Individuals that experienced more than one seizure per month, but less than one seizure per week had more frequent migraines ($p=0.017$). Kelly et al. (2012) cohort study found that 25% of the children with epilepsy in the cohort suffered from migraines compared to 3%-23% of children without epilepsy. In Wirrell & Hamiwka (2006) cohort study found there were migraines in 37.7% ($p=0.05$) of those with benign Rolandic epilepsy and 35.8% ($p=0.05$) of those with cryptogenic/partial epilepsy compared to 11% in the control. Given this information a clinician must consider subclinical seizure activity when evaluating patients who are presenting with migraine symptoms. Overall based on the research, migraines are co-morbid in 12.4%-37.7% of individuals with epilepsies.

The research consistently shows that there is a physiological and incidental overlap of migraines and seizures. Similar pathophysiology and presentation of symptoms makes distinguishing migraine with aura from seizure activity more difficult, but also more important.

Although, multifactorial, the research consistently indicates that migraines are often misdiagnosed and undertreated. Minen (2016) reports only 28% of primary care providers were familiar with the American Academy of Neurology guidelines on preventive treatment of migraines. Viticchi et al. (2010) found in 53% of patients it took five or more years to receive a migraine diagnosis. Dodick et al. (2016) found that only 4.5% of the patients studied were able to complete the three barriers to migraine treatment: accessing medical consultation, obtaining accurate diagnosis, and receiving pharmacological treatment. Once diagnosis was made few patients have reported receiving appropriate/adequate treatment. Lipton et al. (2017) report only 13% of patients who qualify for prophylactic treatment were using it. Similarly, Bigal et al (2008) found that 52% of chronic migraine suffers were unsatisfied with their prescribed treatment. Kalilani et al. (2019) found epilepsies are undertreated as well, with 36.7% of epilepsies untreated three years after diagnosis.

An important aspect of primary care practice is developing differential diagnoses based on all the information gathered through family history, past medical history, symptoms, physical exam, and results of diagnostic studies. In most of the resources available to clinicians, seizure disorder should be on the list of differential diagnoses in migraines with aura. Despite this, diagnostic studies are not typically ordered in cases of migraine. The goal of this research was to determine if EEG would be a valuable tool in the diagnostic work up of a patient presenting with migraine with aura.

As previously outlined, the diagnosis of migraine is typically completed clinically. Although lengthy testing can delay diagnosis and increase costs, an EEG would be the preferred test to rule in or rule out abnormal brain electrical activity as the source of migraine with aura symptoms. EEG changes can often be seen in subclinical epilepsies whereas in migraines there is a lack of habituation (Bianchin et al., 2010). In evaluation of the research there were several studies that show that some individuals that were suffering migraine symptoms were in fact having seizures, which was not evident without the use of EEG.

In a systematic-prospective study of occipital seizures with elementary visual hallucinations, EEG was helpful in making a specific diagnosis but the biggest take away was that all but two of the 1,360 participants (99%) in this study were initially misdiagnosed with migraine with aura, acephalgic migraine or basilar migraine and proper treatment was delayed (Panayiotopoulos, 1999). Another study showed that 20% of the participants with known seizure disorders also had migraine symptoms, with 3% experiencing seizures during or immediately following a migraine aura. There were distinctive changes on the EEG during the migraine aura that preceded the onset of an electrographic complex partial seizure (Marks & Ehrenberg, 1993). Further evidence suggests that EEG may be useful in migraine evaluation, Kollar et al. (2014) found interictal EEG abnormalities in 5% of 100 patients with migraine. Lozeron et al. (2018) found epileptiform discharges on EEG in three patients, one with focal seizure and two with migraine aura. In migraine with aura this represents 15% of the patients examined in that study. Interestingly, in evaluating the prevalence of seizure activity as the underlying cause of migraine symptoms, between 5% and 99% of patients in these studies with migraine symptoms were in fact having seizures.

In using EEG for evaluation of migraine Pisani & Fusco (2004) found excess focal slowing in the delta or theta range localized on the parietal-occipital or temporal regions in the EEGs of all participants of the study with diagnosed migraine with aura and basilar migraine. Bjork et al. (2011) found EEG changes with migraine including frontocentral, temporal and occipitoparietal hemispheric slowing and asymmetry appearing within thirty-six hours of migraine onset with increased power. This is promising information that there are specific changes in EEG seen with migraines but may not be helpful in migraine unless they are experiencing a migraine during the exam. In Brinciotti et al. (2000) research, insight was gained into differentiation of migraine and occipital epilepsies based on specific EEG differences, clinical symptoms, and family history between the groups, which will be reviewed in the clinical application section.

Overall, the research does indicate the use of EEG is able to distinguish migraine from seizure activity in all participants. Although inferences can be made regarding the value of EEG in migraine evaluation, further large-scale studies wound need to be completed to truly know how helpful regular use of EEG would be. If only 5% of individuals with migraine symptoms were caused by abnormal electrical activity, completing EEG on every patient with migraine would not make sense. If, however it occurred in 30% of individuals with migraines, using EEG more regularly may be reasonable. The research I conducted did not provide that information. Certainly, when the clinical presentation is unclear for definitive migraine or there is concern for subclinical seizure activity as the source of migraine symptoms an EEG would be useful.

Conclusion

Based on the research there were several themes that emerged. First, migraines are a significant issue affecting many individuals in the United States and is a common complaint in

the primary care setting. Second, primary care providers may not have adequate knowledge to diagnose migraines, much less be able to differentiate a migraine with aura from seizure activity. Third, there are often significant delays in diagnosis and often suboptimal treatment of migraine symptoms from the patient perspective. This is likely multifactorial but also may further allude to the idea that perhaps seizure activity is being misdiagnosed and mistreated as migraine with aura, at least in some cases.

After evaluation of the information available it is concluded that an EEG is not warranted in most situations of a patient presenting with migraine symptoms in a primary care setting. However, there are some circumstances an EEG would be a helpful tool in patients presenting with migraine symptoms, or intractable migraines. It is the responsibility of the primary care provider to be knowledgeable in identifying patterns of symptoms that are consistent with migraine with aura versus symptoms that are suspicious for seizure activity. This knowledge base would certainly lead to more prompt diagnosis and as well as decreased costs associated with delays in treatment and moreover improve patient outcomes, satisfaction, and quality of life.

Applicability to Clinical Practice

The applicable knowledge gained from my research primarily is that of differentiation of epidemiology, symptoms and family history between migraines and epilepsies.

Migraines occur less often in childhood and elderly and occur more often in women than men. Migraine symptoms persist for longer with pain being the primary symptom. In migraine the visual aura usually involves negative symptoms, slow spreading, and is monochromatic (Bianchin et al., 2010). Migraine with aura (determined as migraine with visual symptoms of zigzag lines, heat waves, blurry vision, or loss of vision) (Ludvigsson et al., 2006). Onset is gradual over minutes and exists towards the periphery of one hemifield and often leaves a partial

alteration in the field of vision (scatoma) and rarely occurs daily (Panayiotopoulos, 1999). Migraine with aura is more likely in individuals who have two or more first degree relatives with a history of epilepsy (Winawer & Connors, 2013). In migraines there are bilateral EEG abnormalities with no changes with photic stimulation and without evident clinical signs (Brinciotti et al., 2000).

Epilepsy occurs more often in children and the elderly and is found equally between males and females. Seizures are relatively brief with additional symptoms of sensory, visual, and motor symptoms. The aura in epilepsy is often shorter, more complex, brightly colored, and sometimes presents with feelings of déjà-vu (Bianchin et al., 2010). Visual hallucinations are typically colored and small circular flashing in a temporal hemifield. These visual hallucinations last for seconds but occur frequently, develop fast and have the same progression each time. Additional symptoms may include eye and head deviation, illusions of eye movement, eyelid repetitive closures, or fluttering (Panayiotopoulos, 1999). Characteristics in epilepsy include a family history of epilepsy, with visual symptoms such as with colored hallucinations and micro/macropsias, unilateral EEG abnormalities, and abnormal response to photic stimulation and clinically are associated with clinical signs in the visual system such as eye deviation and nystagmus (Brinciotti et al., 2000).

If a patient presents with migraine with aura and the etiology, symptoms, and family history is consistent with migraine, empiric treatment, as outline in the literature review, is reasonable. Regarding migraine prophylaxis, Topiramate, particularly long acting, is recommended as a first option. There is evidence that the use of Topiramate significantly improved mean functional disability scores compared to amitriptyline. A second option is

provided with valproic acid which showed a >50% decrease in headache frequency compared to placebo (Parikh & Silberstein, 2019).

Primary care providers need to keep in mind that migraine with aura is associated with up to 3.7- fold increased risk for developing epilepsy. Therefore, if a patient presents with migraine with aura and the etiology, symptoms, and family history are not entirely consistent with migraine or empiric treatment has failed an EEG or neurology referral is warranted.

Additionally, since individuals with known epilepsies do frequently experience migraines, and often do not report symptoms to clinicians, it is important for primary care providers to evaluate for migraines in such individuals. As stated, the International Classification of Headache Disorders (ICHD-II) outlines 3 categories; migraine-triggered seizures (5-15% of patients with epilepsy), hemicrania epileptica (5% of patients with epilepsy), and postictal headaches (10-50% of patients with epilepsy) (Bianchin et al. 2010). Therefore, primary care providers should keep in mind that those with earlier onset of epilepsy have been found to have greater incidence of migraine, and those with longer duration of epilepsy have been shown to have a greater incidence of seizure related headaches (HELP Study Group, 2010). Additionally, the research shows even in the case of seizure disorders, females experience migraine headaches more often than males and individuals that experience more than one seizure per month, but less than one seizure per week have more frequent migraines (Cilliler et al., 2017). If there is comorbidity, it has been found that there is improved seizure control with combination antimigraine and antiepileptic drugs in patients who failed to respond to anti-epileptic drugs alone (Marks & Ehrenberg, 1993). Cilliler et al. (2017) agrees with this, pointing out the varying mechanisms of action in using different antiepileptic medications help inhibit cortical spreading depression resulting in lower frequency of headaches in patients receiving polytherapy.

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