Headaches in Women

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Cambridge
Scholars
Publishing

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This book first published 2019

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-3863-X
ISBN (13): 978-1-5275-3863-4

Cover design by Adam Green

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CHAPTER 1

THE EPIDEMIOLOGY OF HEADACHES IN WOMEN

ARKADY YUSUPOV MD

As per the International Classification of Headache Disorders, 3rd edition, beta version criteria, headache disorders are divided into primary disorders, such as migraine, tension type, trigeminal autonomic cephalalgias; and secondary disorders. Secondary headache disorders are attributable to an underlying condition, i.e. malignancy, infectious, vascular, traumatic, inflammatory causes. The epidemiology of secondary headache is determined by the epidemiology of the underlying cause. This chapter describes the epidemiology of headaches in women, with focus on the primary headache disorders.

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems. Incidence quantifies the number of new cases of disease that develop in a population over a defined period of time. Prevalence is the proportion of a population that has the disease over a given period of time. Prevalence is determined by the average incidence and average duration of disease.

Epidemiology of Migraine

It is well established that the majority of primary headache disorders have a higher prevalence in females than males. Many experience a diminished quality of life, reductions in workplace productivity, and limited participation in and enjoyment of social and leisure activities. Because of the high prevalence and substantial individual burden of migraine, the World Health Organization ranks it second among neurological conditions, after stroke, in terms of years lived with disability.

Specific to the United States, three main studies assessed the epidemiology of migraine in adults. The American Migraine Study- 1 collected information from 15,000 household's representative of the United States population in 1989. The American Migraine Study- 2 used identical methodology in 1999. The American Migraine Prevention and Prevalence study was conducted in 2004. It was the largest epidemiological study conducted, and confirmed the results of the AMS ll. The AMPP study estimated that 35 million United States residents had migraine, translating to nearly 1 in 4 households having someone suffering with migraine. The results of these studies revealed the prevalence of migraine was about 18% in women and 6% in men. Hence, there is a very large sex difference in migraine, with a 3-fold greater prevalence rate among women.

Reviews by Stovner and Jensen summarized a total of 107 publications from 6 continents, including 24 studies in Europe, 12 studies in South America, 12 studies in North America, 10 studies in Asia, 5 studies in the Middle East, 7 studies in Africa, and 3 studies in Australia and New Zealand. These reviews demonstrate that the prevalence estimates are fairly comparable across the world and that migraine differentially affects women during the reproductive period of their lives.

The strikingly higher prevalence of migraine in females compared with males is one of the hallmarks of migraine. Migraine prevalence was highest in those aged 30 to 39 years for both men (7.4%) and women (24.4%). Prevalence was lowest in those aged 60 years or older at 1.6% in men and 5.0% in women. At the other end of the lifespan, prevalence was 4.0% in men and 6.4% in women aged between 12 and 17 years. In both women and men, migraine without aura is more common than migraine with aura.

Few longitudinal studies have assessed migraine incidence, but there have been consistent differences between women and men. Migraine incidence peaked between the ages of 20 and 24 in women and between 15 and 19 years in men. In 2003, Lyngberg and colleagues published a population-based study of the incidence of migraine in a Danish population, which was a follow up to a cross-sectional epidemiology study from 1989. Results revealed the annual incidence of migraine in females to be 1.5 % and in males 0.3%.

Epidemiology of Tension Type Headache

Tension-type headache is the most prevalent of the primary headaches. In the United States, Schwarts and colleagues found the prevalence of episodic tension type headache was 38.3 %. Women had a higher 1-year episodic TTH prevalence than men with an overall prevalence ratio of 1.16. The 1-year period prevalence of chronic tension type headache was 2.2%, and prevalence was higher in women.

Epidemiology of Cluster Headache

Based on epidemiological surveys from the USA and Europe, cluster headache has a prevalence of around 0.1% of the general population. Typically, men are more frequently affected than women, with a male to female ratio of about 3:1, however, this ratio has decreased over the past few decades with more women being diagnosed with cluster headache, and so the accuracy of this historical ratio has been questioned.

Several factors have been discussed regarding this decline. The decline might reflect an improvement in diagnostic accuracy rather than a change in the sex ratio. This improved diagnostic accuracy might be particularly relevant in women, for whom unawareness of the disorder probably led to the frequent misdiagnosis of cluster headache as migraine.

Manzoni reported a decreasing trend of the male preponderance over time in a series of 482 patients consecutively referred to the University of Parma Headache Centre between 1976 and 1995. The ratio of males to females was shown to decrease successively from 6.2: 1 in those patients who had an onset before 1960, to 2.1: 1 in those with an onset between 1990 and 1995. It was suggested that changes in lifestyle factors over the years, such as employment rate and smoking habits, in both sexes might have played a major role in changing the gender ratio of cluster headache.

Epidemiology of Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) has been considered to be predominantly a problem of females. In the initial reported female: male ratio was 7 : 1 (Sjaastad and Dale, 1974), and in a subsequent review of 84 patients (Antonaci and Sjaastad, 1989) the female: male ratio was 2.36 : 1. The case series, assessing prospectively a group of 31 patients (mean age 37 years, range 5–68) with possible PH, were identified at the National

Hospital for Neurology and Neurosurgery and the Hospital for Sick Children, Great Ormond Street from May 1995 to January 2007, and attended the outpatient departments between January 2004 and January 2007. Results did not find a clear female preponderance. The prevailing view of PH as a condition of females may arise from misdiagnosis of males with PH as cluster headache, as it is the more common problem and recognized to have a male preponderance.

Epidemiology of Hemicrania Continua

Hemicrania continua is classically considered a disease with a female preponderance. In a 1991 review by Bordini et al., the female to male ratio was 5:1.5. This female preponderance reduced to 2.8:1 in Peres et al.'s review in 2001. The current pooled analysis of 472 patients revealed female to male ratio of 1.8:1.

In summary, headache disorders are divided into primary and secondary disorders. Tension type headache and migraine are the most common primary disorders. The epidemiology of migraine was assessed via three main studies revealing prevalence of migraine to be about 18% in women and 6% in men. Regarding cluster headache, men are more frequently affected than women, with a male to female ratio of about 3:1 although, this ratio has been decreasing over the past few decades. Epidemiological studies revealed that paroxysmal hemicrania (PH) has been considered to be predominantly a problem of females and hemicrania continua is considered a disease with a female preponderance. Secondary headache disorders are attributable to an underlying condition, i.e. malignancy, infectious, vascular, traumatic, inflammatory causes. The epidemiology of secondary headache is determined by the epidemiology of the underlying cause.

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CHAPTER 2

MIGRAINE AND DISPARITIES OF CARE

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Introduction

There have been numerous studies that reveal disparities in neurologic health care access and utilization for minorities, people in lower socioeconomic groups, and those with less education.[1] African Americans and Hispanics were significantly less likely to see an outpatient neurologist than Caucasians (Saadi, 2017). In 2011, the World Health Organization declared migraine the sixth highest cause of disability worldwide (Befus, 2018). Several studies of patients with migraine have shown disparities in diagnosis and treatment due to gender, ethnicity/race, and socioeconomic status (Befus, 2018). This chapter is a review of the literature regarding disparities in migraine treatment. Understanding the issues resulting in disparities of care is critical to formulating potential solutions as well as identifying future goals for improvement.

Socioeconomic Status and Disparities in Care

Prevalence

Migraine is more prevalent in people in lower socioeconomic groups and is associated with worse outcomes (Befus, 2018), (Charleston, 2018), (Stewart, 2014).

Migraine prevalence has been noted to be inversely related to household income (Stewart, 2014), (Lipton, 2013), (Wilper, 2010). In the American Migraine Prevalence and Prevention (AMPP) Study, an annual household income of more than $90,000 was associated with a migraine prevalence of 13.6% in women and 4.2% in men. When household income was less than

$22,500, migraine prevalence was nearly twice as high, 20.1% in women and 8.8% in men (Charleston et al., 2018).

Several studies have shown that there is a higher prevalence of migraine among people who are unemployed, those with lower family income, as well as those with a lower education (Befus, 2018), (Stewart, 2013), (Charleston et al., 2018). In a cross-section study of 37,000 participants in the Women's Health Study, low socioeconomic status was associated with an increased prevalence of all headaches including migraine. Women in low socioeconomic groups also had an increased frequency of migraine attacks (Winter, 2011). In addition, low socioeconomic status is believed to be an important factor in increased severity of migraine, poorer treatment outcomes, and the greater degree of negative impact on quality of life (Charleston, 2018).

The reasons for the increased migraine prevalence and frequency noted in people with low socioeconomic status are likely multifactorial. People in lower socioeconomic groups may be at higher risk for migraine. Psychosocial stress including financial difficulties, which are more common in the low socioeconomic groups, may contribute to migraine onset as well as attack frequency (Stewart, 2013). Food insecurity is reported twice as frequently by people with migraine (Befus, 2018). Stressors including childhood traumas, domestic violence, and abuse are related to migraine onset in adulthood (Befus, 2018). In addition to the increased risk of migraine in lower socioeconomic groups, some believe that migraine leads to lower socioeconomic status due to loss of productivity. Both mechanisms are likely to play a role. Inadequate insurance further worsens the impact of migraine on low income families.

Medical Evaluation and Treatment

Migraine is underdiagnosed and undertreated particularly in people in lower socioeconomic groups (Befus, 2018). Migraine diagnosis was more likely in those with higher annual household incomes and among those with health insurance (Lipton, 2013). Optimal migraine management requires appropriate medical consultation, accurate diagnosis, and appropriate treatment. In a 2013 study by Lipton et al., the greatest barrier to optimal migraine treatment and management was obtaining a medical consultation. Using data from the AMPP study, they found that health insurance is an important predictor of consultations with doctors for migraine care (Lipton, 2013). In fact, people with health insurance are nearly twice as likely to receive a migraine diagnosis. Part of the issue is the difficulty for the

uninsured and Medicaid insured population to access optimal health care (Befus, 2018). Many of the underinsured/uninsured patients are seen in large clinic settings and have limited access to subspecialists. In addition, many of these patients use the emergency room for their care rather than using office visits (Wilper, 2010).

Once migraine patients reach the practitioner, receiving appropriate therapies continues to be affected. Household income and insurance status were the strongest predictors of using appropriate migraine specific therapy (Befus, 2018), (Charleston et al., 2018). The uninsured and those with Medicaid receive substandard therapy for migraine compared with patients who have private insurance (Wilper, 2010). Treatment in the emergency room, where care is mostly obtained, is suboptimal for migraine (Wilper, 2010). It often consists of opioids, which are not recognized as proper treatment by migraine specialists (Nijjar, 2011). In one study, only about a third of patients seen in the emergency room were given discharge medications and less than half were told to follow up with a physician (Wilper, 2010). The National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey revealed that even when patients were appropriately diagnosed with migraine, uninsured or Medicaid insured patients were less likely than those privately insured to receive abortive or prophylactic therapy (Wilper, 2010). This disparity in treatment may also be related to or compounded by the high cost of many migraine medications.

Ethnicity and Disparities in Care

Prevalence

There are some variations in reported prevalence of migraine in various ethnic groups. Migraine is more common in Caucasians (20%) than African Americans (16%) (Nicholson, 2008). The National Health Interview Survey (NHIS) produced similar trends in prevalence data with slight variation in exact numbers. Severe headache or migraine occurred in 15.5 % of Caucasians, 14.5% of Hispanics and 14.45 % of African Americans. Migraine prevalence was twice as high for women across all ethnic groups. Hispanic women had the highest and white males the lowest prevalence of chronic migraine according to data from the American Migraine Prevalence and Prevention study (AMPP) (Loder, 2015).

The characteristics of migraine differ amongst ethnic groups. African Americans are more likely to experience debilitating migraine headaches than Caucasians. Multi-database searches and analyses reveal that African Americans have more frequent and severe migraines and these are more likely to become chronic. Migraine in African Americans is associated with more depression and lower quality of life compared to Caucasians (Charleston, 2018), (Heckman, 2015).

Medical Evaluation and Treatment

Ethnicity affects evaluation and treatment, as well. Migraine is underdiagnosed and undertreated in people of color (Befus, 2018). In one study, 131 adult patients with migraine were evaluated for utilization of the healthcare system for care, diagnosis, and treatment. The study also evaluated the level of mistrust of the healthcare system and quality of communication with the provider. More than 25% of Caucasians and 50% of African Americans had never seen a physician for headache care despite having moderate to severely disabling migraines. Even after controlling for socioeconomic status, the study found that African Americans were less likely to use the health care system for headache management, less likely to have a precise headache diagnosis, and less likely to receive appropriate treatment with acute migraine medication (Befus, 2018), (Nicholson, 2008), (Gibbs, 2003).

Although not all studies agree, several studies find that minority patients with migraine may not be receiving adequate care in comparison to Caucasians with migraine (Loder, 2015). Data collected from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) shows that Hispanics with migraine have the lowest rate of utilizing the healthcare system for migraine management (Loder, 2015). Furthermore, analysis of data from the NAMCS and NHAMCS revealed that Hispanics receive fewer prophylactic medications regardless of insurance status (Wilper, 2010).

Part of the reasons for the substandard levels of care may be related to trust and communication issues with providers. The African American population were noted to have less trust in the medical community and a sense of poor communication with their providers (Nicholson, 2008). This is likely the cause of treatment non-compliance. In fact, African American patients discontinue treatment early. This is regardless of

socioeconomic status (Heckman, 2015). For the Latino/Hispanic patients, language barriers may also play a role.

Gender and Disparities in Care

Prevalence

Women are affected with migraine twice as often as men (Befus, 2018). In the United States, data suggests that migraine affects 20.7% of women, compared to 9.7 % of men and was the third leading reason for emergency room visits in women aged 15-64 in 2014 (Befus, 2018).

In the Migraine in America Symptoms and Treatment study (MAST), women were more likely to report frequent episodic migraine and chronic migraine compared to men (Lipton, 2018). The Baltimore County study found migraine to be prevalent at rates of 20.4% in white females compared to 8.6% of white males and 16.2% black females compared to 7.2% black males (Loder, 2015). Other population-based studies report 15-18% of women and 5-7% of men have migraine (Lipton, 2013).

The migraine experience is different amongst men and women. Some believe that it may lead to negative implications for women, pain, and the need for treatment (Befus, 2018). Women become incapacitated by the symptoms of nausea and vomiting. They often feel like they lose control over their lives. Women suffer guilt over missed work days or family events and/or household responsibilities. According to analysis of the AMPP study, women are more likely than men to report missing at least one day of housework or that their ability to complete housework decreased by more than 50% due to their migraines. Women also miss more social gatherings (Buse, 2013). A study by Kneipp et al. had similar findings. In evaluating headache and health related job loss, they found that a low-income woman with headache was twice as likely to lose her job in the year prior (Kneipp, 2014). The majority of MAST respondents reported moderate to severe intensity, pounding or throbbing quality, and worsening with activity. Women differed from men most notably by increased likelihood to report unilateral pain and disability. Based upon the Migraine Disability Assessment test (MIDAS), women were more likely to report pain grade of IV (most severe disability) compared to men (25.8 % versus 19.4%, respectively) (Lipton, 2018).

Migraine associated symptoms such as nausea, photophobia, phonophobia, osmophobia, and allodynia are significantly more common in women than

men (Lipton, 2018). Women were more likely than men to experience nausea and allodynia at rates of 76.2% versus 67.5% and 43.7% versus 29.5%, respectively. This may all contribute to why women are more likely to report disability and poor treatment optimization (4.1% of women reported "very poor" compared to 2.9% of men) (Lipton, 2018).

Medical Evaluation and Treatment

It is a commonly held belief that women consult physicians more frequently than men for migraine (Hunt, 2011). Eleven publications were reviewed for gender differences in consultation rates for headache. All of them reveal that women are more likely than men to seek out consultations for their migraines (Hunt, 2011).

Regardless of rates of seeking care, women were significantly more likely than men to be diagnosed with migraine, especially chronic migraine. In fact, women who consulted health care providers were twice as likely to receive a chronic migraine diagnosis compared to men (Dodick, 2016). This may in part be related to the bias that health care providers know that migraine is more common in women (Lipton, 2013).

The attitudinal barriers to care of migraine in women include the sense that migraine is a "women's disorder" and that women complain more. It leaves many migraineurs with doubt about their diagnosis with an invisible disease (Rutberg, 2012). A group led by Hunt alludes to physicians feeling that women have lower tolerance for pain compared to men. This group also notes physicians' tendencies to focus on psychological issues/explanations for symptoms when seeing a female patient (Hunt, 2011).

Many women are prepared with abortive medications in their purses or carry on at all times. However according to a cohort reviewed by Rutberg and Ohrling, women appear afraid to use medications due to the short and long-term effects and/or side effects of medications. Many women even questioned whether their ailment deserves a prescription treatment, again alluding to the "women's experience" of an invisible disease (Rutberg, 2012).

The MAST study investigated both acute and chronic management. Nonsteroidal anti-inflammatory drugs (NSAIDS) and triptans were most commonly used for acute management. Interestingly, women were more likely to use triptans (women, 17.7% versus male, 14.3%) and men were more likely to use opioids (men, 14.5% versus women, 9.2%, P<.001) and

ergot alkaloids (men, 2.0 % versus women, .6%, P<.001) (Lipton, 2018). Of MAST study responders, 10.6% used nasal sprays, men more often than women (13.6 % vs 9.4%) and 4.7% of respondents used injectable forms (Lipton, 2018). Opioids are not considered appropriate management amongst migraine specialists (Dodick, 2016). Despite potentially inappropriate treatments, the MAST study revealed that men were more likely to be satisfied with their migraine management (Lipton, 2018).

Although the CaMEO study did not find statistically significant differences in migraine treatment based upon gender, the MAST study revealed that preventative migraine management is lacking for women compared to men. Men were more likely to receive oral prescription preventative medications (14.5% versus 10.4%) as well as OnabotulinumtoxinA (4.1% of men compared to 2.2% of women) (Lipton, 2018).

There are many potential reasons for other gender disparities in care. It is possible that fear amongst women towards using medication may be influencing the choice of treatment and therefore limit the treatment success. Men appear more likely to seek the stronger versions of treatment, including prescription rather than over-the- counter medications or parenteral administration. This may mean they are more likely to treat the migraine at an earlier time and positively affect treatment outcomes. Since women are more likely to suffer from associated symptoms like nausea and vomiting, providers should discuss abortive options more carefully. More discussion regarding possible routes of administration based on associated migraine symptoms, and the timing of use would help alleviate this discrepancy in migraine treatment for women. Education regarding the safety and benefits of appropriate migraine acute or preventive treatment is essential particularly for women with migraine.

Addressing Disparities of Care

Migraine awareness must increase amongst patients and medical providers. Increasing awareness about seeing a specialist for migraine care and educating patients about available treatment options would better allow patients to make informed decisions about their health (Lipton, 2013).

Efforts should be made to improve patient-physician communication, which can be particularly problematic with regard to cultural sensitivity. Translation services for those speaking different languages are also critical. Focused research and public health efforts are required to

encourage neurological consultations. Improvements in these factors may decrease the level of mistrust in the healthcare system and are essential to promote greater utilization of health care systems (Nicholson, 2008).

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CHAPTER 3

WHAT IS MIGRAINE?

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Just like diabetes and hypertension, migraine is the phenotypic manifestation of what are likely to be multiple processes.

Most cases of migraine are transient events, and those with aura have associated focal neurological complaints. At times, this diagnosis can be confused with other neurological conditions, which are also transient. These include strokes and transient ischemic attacks, which can be associated with headache. Epilepsy can cause focal neurological complaints and seizures can sometimes be associated with headache. Multiple sclerosis on occasion causes transient complaints, and depending on the location of the demyelinating lesions, can lead to various head and neck pains.

In neurological practice, migraine is far more prevalent than multiple sclerosis, epilepsy, Parkinson's disease, stroke, and Alzheimer's disease. Furthermore, it is a leading cause of disability. In 2016 the Global Burden of Disease Study, which reviews mortality and disability from major illnesses, injuries, and risk factors, and published in Lancet, listed migraine as the second leading cause of disability years worldwide, only behind low back pain (Vos 2016). By this same study, migraine was noted to be a more prevalent disabling illness than iron deficiency anemia and major depression. In participants ages 15 to 49, migraine was considered the leading cause of disability (Vos 2016). Much of this is due to the fact that migraine is highly prevalent in this age range, seen in 18% of females and 6% of males (Lipton 2001). The peak prevalence of migraine is in the late 30s and early 40s (Lipton 2007). This represents a time when individuals are likely to be most successful in terms of their careers and personal lives; having migraine clearly interferes with these processes. It used to be stated that migraine is a disease of the rich but since migraineurs often suffer from

absenteeism and presenteeism, they often undergo a downward socioeconomic drift.

The natural course of a typical migraine attack involves three or four phases, although the order and extent of these is not invariable. Many migraines begin with a prodrome, which can occur a day or two before the attack. Some common prodromal symptoms include cold hands and feet, food cravings, yawning, and frequent urination. About 20% these patients will develop aura. Often following the aura, the headache of migraine may develop which can be unilateral or bilateral, and can be pressure-like or pulsatile in quality. The aura, if present, can develop during the headache phase, or multiple auras in sequence can develop. The most sensitive feature of a migraine headache, although not the most specific, is that the pain worsens with routine movement, which is why patients often try to remain immobile during an attack. The headache in migraine can last 4 to 72 hours, although there is a great deal of variability. In the beginning of an attack, the pain may be centered around one eye or at the temple but can be generalized, and as the attack advances the pain often can become generalized. This is likely a result of the attack transitioning from activation of the first order neuron to also involve the thalamus. The final phase of the migraine is the postdromal phase, which can last anywhere from hours to days after the head pain resolves. The postdrome often includes fatigue, nausea, mental fogginess, poor concentration, muscle tenderness, and tenderness of the scalp.

The ICDH-3 criteria for migraine with and without aura are:

Migraine without Aura

Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. Unilateral location
    2. Pulsating quality

3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

Migraine with Aura

Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:
1.Visual
2.Sensory
3.Speech and/or language
4.Motor
5.Brainstem
6.Retinal

C. 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

D. Not better accounted for by another ICHD-3 diagnosis.

Most migraine auras are visual, but only two thirds of patients have solely visual auras; many will report a visual aura along with sensory or motor components as well. One common, and perhaps pathognomonic sensory aura, is cheiro-oral numbness, where there is numbness involving the cheek or lips and hand. Sensory auras typically involve tingling followed by numbness. This is reflective of the wave of cortical spreading depression, which activates first, thereby causing positive phenomena. Then as it passes,

the cortical activity is decreased, which results in negative phenomena. Other aura symptoms include aphasia, neglect syndromes, and a variety of vestibular symptoms. (Russell 1996)

Even though migraine is highly prevalent and highly disabling, the diagnosis rate by healthcare practitioners is exceedingly low. In 2007, it was shown that 56% of those with the diagnostic criteria for migraine were actually diagnosed as having this problem (Diamond 2007). When analyzing which diagnoses those migraineurs had been given prior, 32% were told they had tension-type headaches, and 42% were told had sinus headaches (Lipton 2001). Since a diagnosis of "sinus headache" is more likely to be made in the United States, it is possible that other countries have better statistics. However, the Landmark Study was a prospective multicenter international study in the primary care setting, involving patients who consulted their doctors for the complaint of headache. The doctor diagnosed patients via their customary methods and an expert panel, after chart review, made a final headache diagnosis. The conclusion was that when one went to primary care doctor with a complaint of headache, 76% of the time they had migraine and 18% of the time they had migrainous headaches, 3% had episodic tension headache and only 3% of the remainder had something else (Tepper 2004).

In 1980, Raskin and Appenzeller proposed the concept that migraines were in a continuum, representing migraine with aura on one end of the spectrum, and chronic tension-type headaches on the other end of the spectrum. This concept is understandable when migraineurs consult a doctor for their "many types of headaches" (Raskin 1980).

Why is there so much confusion with the diagnosis of tension-type headache and migraine? Part of this may stem from the fact that neck pain is highly prevalent in migraine, even though it is not considered in the in the International Classification. Kaniecki showed that 75% of migraineurs had neck pain, and it can be either unilateral or bilateral (Kaniecki 2004). He also found that 85% of those with neck pain were diagnosed with "tension headache" or "stress headache" despite the fact that they met the criteria of the International Headache Society for migraine. The trigeminal nucleus caudalis, which becomes activated during a migraine attack, extends from C2 to C4, although there is some individual variation. Upon trigeminal nucleus caudalis activation, the subsequent pain can be referred to any of three branches of the trigeminal and/or cervical nerves and thus pain can be perceived on one or both sides of the head, around the eyes or sinuses, and in the posterior area of the head and neck (Messlinger 2006). The presence

of neck pain, therefore, does not necessarily mean that the individual has "tension-type headache."

The other common misdiagnosis in migraineurs is "sinus headache." Chronic sinusitis is rarely associated with head pain. Acute sinusitis can cause headache or facial pain, but it is typically associated with fever and purulent nasal drainage. Cranial parasympathetic nerves become activated during a migraine attack, which can cause eye tearing and nasal congestion, but not purulent drainage. Barbanti evaluated the prevalence of autonomic symptoms specifically eye tearing and nasal congestion among migraineurs. 46% of those participants with migraine had reported experiencing autonomic symptoms, which included eye tearing, nasal congestion or both (Barbanti 2002). Schreiber found that 80% of those with the diagnosis of "sinus headache" met the IHS criteria for migraine (Schreiber 2004). It is important to recognize that this study was performed in the United States where the diagnosis of "sinus headache" is frequently made.

An oft-quoted physiologic explanation of migraine was a theory by Harold Wolff. This suggested that the auras of migraine were due to cerebral vasoconstriction and that the headache was due to cerebral vasodilatation (Wolff 1948). Ergotamine, a powerful vasoconstrictor, was useful in terminating an attack of migraine (Tunis 1953). In fact, there are significant changes in cerebral blood flow in the cortex in migraine (Cutrer 2006). However, more careful evaluations of cerebral blood flow during aura and the headache phase, showed a less than tight relationship between hypoperfusion and aura and hyperperfusion and headache. (Olesen 1990) Moskowitz showed that trigeminovascular neurons have an important influencer on the size of these arteries and, when activated, also caused an inflammatory response called "neurogenic inflammation" (Moskowitz 1993). Brainstem and subcortical structures increasingly became implicated in the production of a migraine (Bahra 2001).

Much of the pathology of migraine does appear to occur from the meninges and nociceptors which innervate the blood vessels of the pia, arachnoid and dura (Olesen 2009). The sensory innervation of these structures is from the trigeminal and vagus nerves, and to some degree upper cervical spinal nerves. The first division of the trigeminal nerve largely supplies the supratentorial dura. The location of pain experienced during a migraine attack could conceivably be referred from these structures. It is been suggested that the pulsatile nature of migraine pain does not coincide with pulsations of arteries but rather pulsations of cerebrospinal fluid that would not normally be felt except in a situation with sensitized meninges. Cortical

spreading depression CSD), a wave travelling posteriorly to anteriorly in the cortex at a rate of 2-6 mm/ minute, correlates with aura propagation, and was first described by Leão. (Leão 1944). Neurons and glia are depolarized during CSD and therefore activated, then inhibited (Smith 2006). Correlating with this, migraine auras often begin with a positive phenomenon (like teichopsias or scintillations), followed by a negative phenomenon, like a scotoma. Slow moving waves of approximately the same speed during a migraine are seen on magnetoencephalography and blood oxygen level dependent (BOLD) MRI studies (Hadjikhani 2011). It is less clear whether patients, who do not have an aura, develop this same wave, as it is difficult to image a spontaneous, not a triggered attack. However, one case did reveal typical spreading hypoperfusion without the experience of an aura (Woods 1994). Cortical spreading depression can be associated with a release of a variety of chemicals into the meninges. The meninges are innervated by the first division of the trigeminal nerve, which may explain why the pain is often experienced in the eye and the temple. As an attack proceeds, the pathway involves the second-order trigeminal neurons between the trigeminal nucleus caudalis and the thalamus. Because the thalamus is associated with convergence of sensory neurons, the pain may become more generalized once the activation reaches the thalamus (Noseda and Burstein 2013).

Perhaps if a migraine begins in the trigeminal nucleus in the brainstem it then activates the dural arteries and leads to dilation. At the same time, chemicals such as CGRP, neurokinin A, norepinephrine and serotonin are also released.

A fundamental concept of migraine is that these individuals with migraine have a “hyperexcitable brain” (Hargreaves 1999). This is supported by the fact that many triggers of migraine attacks involve changes in routine. For example, events like oversleeping or undersleeping, missing a meal, dehydration, stress, and relaxation from stress all have been documented as known triggers for migraineurs, but these things do not necessarily trigger headaches in non-migraineurs. Hormonal changes during menstruation are also potent triggers for migraines as well. Patients with migraines are more easily triggered into cortical spreading depression when the chemical milieu is changed, even if slightly so, hence supporting the theory of the hyperexcitable brain. Phosphene generation with transcranial magnetic stimulation, lights similar to those seen in migraine, are generated in migraineurs at a low threshold, when compared to those without migraine (Aurora 2003). Likely genetic factors play a role in the susceptibility for this wave. Although most of this is derived from known genes affecting rare

forms of familial hemiplegic migraine, several others as well as single nucleotide polymorphism (SNPs) are known to convey a susceptibility to migraine.

Aside from cortical spreading depression, which involves neurons, there may be an analogous wave that involves microglia and astrocytes. Glia communicate through intracellular calcium waves (Charles 1998). The oligemia that has been demonstrated to spread in a migraine often extends well beyond the distribution of the brain explaining symptoms. This raises a question that this oligemia may not just involve neurons, but may involve glia or other cell types. Glia, thought in the past to be just support cells for neurons, have many other important functions. Among these roles, glial cells may redistribute and buffer abnormal regions of potassium, magnesium and excitatory amino acids. Whereas epilepsy most commonly involves the temporal lobe, the occipital lobe is a vulnerable area in migraine, and often the site of early cortical spreading depression. The visual cortex is the brain region with a higher neuron/astrocyte ratio. It also might reflect differences in metabolic coupling between neurons and astrocytes in this region. Perhaps astrocytic involvement in this region lowest in astrocytes explains why the occipital cortex is easily activated, particularly in migraine with visual aura, whereas the temporal lobe is more often involved in epilepsy (Gonzalez 2013).

There are various neuropeptides that have been implicated in migraine attacks and the pathophysiology of migraine. There has been a great deal of interest in calcitonin gene-related peptide (CGRP), with several CGRP monoclonal antibodies and small molecule CGRP antagonists becoming available for the prevention of migraine. This peptide appears to be a good biomarker for migraine although may well be involved in many other headache types. CGRP is a main neuropeptide that is released when trigeminovascular neurons are activated. If CGRP is infused into an individual with a history of migraine, a migraine can be induced (Cernuda 2013). During that migraine, CGRP levels increase in the cerebrospinal fluid, jugular venous blood, and saliva (Alemam 2017). CGRP is also chronically elevated in patients with chronic migraine (Cernuda 2013). CGRP has many physiologic actions, which may be relevant to migraine production. Mast cells, which are prevalent in the meninges, are degranulated when CGRP is administered, thereby increasing local inflammation and activating second-order neurons in the trigeminal system, resulting in cerebral vasodilatation.

Glutamate, the most prevalent excitatory amino acid, is increased during a migraine, and glutamate can increase cortical excitability. Neurons containing glutamate are found in multiple neuronal pathways that appear to be important in the production of a migraine, and CSF glutamate is elevated in those with chronic migraine (Gallai 2003).

Nitric oxide, a potent vasodilator, may also be relevant in migraine pathophysiology, as nitric oxide donors will induce migraine in individuals with a history of migraine. Fibers containing nitric oxide synthase are found in parasympathetic fibers, trigeminal sensory fibers and around cranial cerebral blood vessels. Nitric oxide species also are elevated in the cerebrospinal fluid of patients with chronic daily headache.

There appear to be multiple mechanisms by which the phenotype of migraine can be generated. In the same way, there is no single treatment that is universally effective. Newer treatments try to exploit final common pathways which produce migraines, particularly as individual's genetic and genomic predispositions cannot be routinely identified.

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