Case-Based Biopsychosocial Approaches to Headaches

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Edited by

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CHAPTER 1

HEADACHE EPIDEMIOLOGY AND DISEASE BURDEN

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1.1 Introduction

Headache is among the most frequent complaints encountered in medical practice and constitutes an important health problem owing to its high prevalence, disability and financial cost. In spite of some regional variations, headache disorders impact individuals across all age groups, ethnic backgrounds, socioeconomic status, and and geographical regions. The lifetime prevalence of headache disorders in many populations is over 90%. Globally, almost 50% of adults experiences an active headache disorder (1). The 1-year prevalence of headache varies between 29% and 77% in adults; this rate is 40-83% for women; is 19-69% for men (2). In European countries, the lifetime prevalence has been found to be 35-96%. In the report of six studies conducted in Europe, the 1-year prevalence of headaches was reported as 50.5%, with being more common in women. Prevalence peaks during an individual's most productive years, typically between ages 25 and 55, leading to significant decline in productivity (3).

Although most headaches are not a symptom of a serious illness, they cause important levels of disability. Primary headache disorders are listed among the top ten medical conditions that cause significant disability in the general population, with tension-type headache (TTH) and migraine being the most prevalent types. In the 2019 Global Burden of Disease (GBD) study, headache disorders were identified as the 14th major contributor to disability-adjusted life years (DALYs) across all age groups

and both genders, and they ranked 10th among females specifically. Headache disorders were the cause of 46.6 million years lived with disability (YLDs) worlwide, 5.4% of total YLDs. Among the listed causes of YLDs, headache disorders were ranked third for all ages and both genders, second among females aged 15-49 years, and first in all young adults (4,5).

1.2 Migraine

Epidemiology

Migraine is a chronic and debilitating neurovascular disorder that can last a lifetime, impacting over 1 billion people globally. A longitudinal study in Denmark over 12 years estimated the overall incidence of migraine to be 8.1 cases per 1,000 person-years, revealing a male-to-female ratio of of 1:6 (6). The incidence rates decreased with age, peaking in the age group of 25 to 34 for females (23 per 1,000 persons-years) and for males (approximately 10 per 1,000 person-years). The lowest rates for both genders were observed in the 55 to 64 age group, falling below 5 per 1,000 person-years. In the American Migraine Prevalence and Prevention study (7), the cumulative lifetime incidence was found to be 43% in females and 18% in males. Incidence rates were highest in women aged 20 to 24, at 18.2 per 1,000 person-years, whereas for men, the peak occurred in the age group of 15 to 19, with an incidence of 6.2 per 1,000 person-years. Nonetheless, the mean age of onset was somewhat earlier in women, at 23.2 years, compared to 25.5 years in men. Migraine onset occured before the age of 35 in about 75% of both genders. In a 5-year longitudinal study in Turkey, the incidence was determined as 2.38% (2.98% for women and 1.93% for men) for migraine and as 0.066% for chronic migraine (8).

The 1-year prevalence of migraine has been estimated to be 15% in the world (9,10). The Eurolight project, which gathered data from nine European countries, declared a one-year prevalence rate of 35% after adjusting for sex (11). In comparison, estimates from the USA indicated a one-year prevalence of 12–13%, which has remained stable over time (12). The GBD 2016 study reported a global prevalence of 14.4%, while the GBD 2019 study indicated a prevalence of 15.2% (13). The age-standardized prevalence of migraine increased by 1.7% from 1990 to 2019 globally, and there were 1.1 billion prevalent cases in 2019 (14). In an epidemiological study carried out in Turkey, the migraine prevalence was determined to be 16.4% (15). It has been estimated that there are 3,000 migraine attacks daily for every million individuals in the general

population (16). Migraine with aura impacts 5% of the adult population, with 90% of auras being visual.

Migraine prevalence varies according to geographical regions. A meta-analysis involving 302 community-based studies found migraine prevalence rates of 16.4% in Central and South America, 9.7% in North America, 11.4% in Europe, 10.4% in Africa, and 10.1% in Asia (17). In tha data of GBD 2016 study, the prevalence was highest in Nepal and lowest in China (10). In terms of race, a study conducted in the US indicated a higher prevalence of migraine among white individuals compared to blacks (12). The discrepancy in prevalence highlights that Genetics may play a role in predisposing individuals to migraine attacks, however environmental factors significantly influence this predisposition (18).

The prevalence of migraine is age- and sex- related. It is 2-3 times more prevelant in females than in males (19). Migraine prevalence ranges from 5% to 9% in men and from 12% to 25% in women (20). In the 2016 GBD study, the age-standardized prevalence rate for migraine was notified to be 18.9% in women and 9.8% in men (10). The prevalence increases in adolescence and early adulthood and peaks among individuals in their late 30s (21). There is usually no gender difference in prepubertal children (19). In a study conducted in school-age children (6-17 years) in Turkey, 1-year migraine prevalence was reported to be 26% (7% definite, 19% probable) (22), however in a US study, a 1-year prevalence among adolescents was found to be 6%, excluding those with possible migraine (23). Prevalence rates in older adults are reported to be almost 7% in people aged between 60 years and 69 years, and almost 4% in people aged 70 years or older (24).

The worldwide prevalence of chronic migraine is estimated to be 1.4–2.2%. A study carried out in Turkey detected that the prevalence of chronic migraine, including patients with medication overuse, was 1.7% (25). Chronic migraine affects approximately 8% of all patients with migraine (26). Every year, among those with episodic migraine, 2.5% progress to a chronic migraine (27). Even though, a gradual increment in the frequency of attack might occur spontaneously, it is frequently exacerbated and/or induced by overuse of acute headache medications and/or caffeine (28). About half of the individuals with chronic migraine are considered to be caused by medication-overuse headache (29).

Studies conducted among different income levels have reported no significant relationship between migraine prevalence and socioeconomic status (10,30). Nevertheless, two population-based studies in the U.S. revealed a higher prevalence of migraine among individuals with low

household incomes compared to those with higher incomes (12,31). In Russia and Georgia, poverty was shown to be associated with disorders characterized by headaches of 15 days or more per month (9).

There is a genetic predisposition for developing migraine. First-degree relatives of individuals with migraine without aura are about twice as likely to experience migraine without aura, while first-degree relatives of migraine patients with aura have a likelihood that is about four times greater than the general population for experiencing migraine with aura (2,32). Twin studies further suggest that genetic factors significantly contribute to the development of migraine (33).

Several risk factors associated with migraine include being young, female, having a family history of migraine, lacking vocational education, experiencing a high workload, and frequently suffering from TTH (6). Individuals with migraine tend to experience a higher prevalence of various conditions compared to the general population. Neurological comorbidities include sleep disorders, epilepsy, restless legs syndrome, stroke, and multiple sclerosis. Psychiatric comorbidities encompass anxiety, depression, panic disorder, post-traumatic stress disorder, bipolar disorder, and suicidality. Other comorbid conditions include asthma, allergic rhinitis, myocardial infarction, patent foramen ovale, temporomandibular joint disorders, Raynaud phenomenon, fibromyalgia, low back pain or localized muscle pain, irritable bowel syndrome, obesity, hypertension, and diabetes (19,27). Overall, comorbidities are more frequently related to chronic migraine than episodic migraine, which may contribute to the risk of migraine progressing to a chronic condition (9).

Burden

Migraine is a significant important public health issue due to its impact on both individuals and society as a whole. It has a substantial impact on the individual's economic situation, family, social, and leisure activities, as well as work and school activities, household work and chores (3). The burden can be associated with severe headache, accompanying symptoms, interictal fear of attacks and associated comorbidities. The GBD 2016 study reported that migraine resulted in 45.1 million years lived with disability (YLDs), representing 5.6% of the global disease burden and surpassing the combined total of all other neurological disorders (1,34). YLDs were determined as 20.3 million in the female population between the ages of 15-49. Migraine is the primary cause of disability among individuals aged less than 50 worldwide, particularly affecting women. In the GBD 2019 study, migraine was the second causes of disability in the

world for both sexes and for the all range ages and first among young women (4,35). Additionally, migraine-related YLDs were reported to be 42.1 million; 26.4 million for women and 15.6 million for men, and to cause 4.8% of the total YLDs. Headache disorders are responsible from 88.2% of the total burden of the disease (4).

Highly personal impact of migraine was demonstrated by a large study conducted in Europe. During a three-month period, 28% of females and 17.7% of males reported losing more than 10 days of activity. On average, both men and women lost nearly one workday per month, with men missing about one day of housework and women losing approximately two days of housework each month. Additionally, men lost about one day of social time each month, while women lost an average of 1.5 days (11). Data from the U.S. demonstrated that individuals with migraine experienced a substantial increase in absenteeism from work or school due to their headaches, resulting in more than a 50% reduction in productivity over the past three months (36). Migraine affects not only migraineurs, but also their spouses and children.

Patients with chronic migraine have a higher level of headache-related disability compared to those with episodic migraine. In the Chronic Migraine Epidemiology and Results study, moderate to severe disability, as indicated by MIDAS scores of grade III or IV, was reported in 71% of men and 82.6% of women with chronic migraine, compared to 26.7% of men and 37.9% of women with episodic migraine (37).

Migraine creates a significant economic burden because of both direct and indirect costs. Direct costs include physician office visits, emergency room visits, diagnostic tests, blood tests, prescriptions, care of comorbid conditions, and inpatient hospitalizations constituted the direct costs. Indirect costs encompass factors like lost work time and decreased productivity. The annual cost of headaches is estimated to be $20 billion in the USA and $27 billion in Europe (3). In Europe, the financial costs associated with migraine in 2011 were estimated to range from €50 billion to €111 billion, with 7% attributed to direct costs and 93% to indirect costs. Two-thirds of indirect costs were productivity losses. Direct healthcare costs due to migraine were €1222 per person. In the USA and Canada, direct healthcare costs averaged $383 over three months for episodic migraine and $1,036 for chronic migraine (38). The total indirect cost related to migraine in the USA, has been estimated at $19.3 billion, 81% of which is attributable to absenteeism (39). In the USA, those suffering from migraine missed nearly 9 more days of work per year compared to individuals without migraine, resulting in an estimated extra cost of $2,350 per affected person in 2019. This absence from work

represented roughly 4% of the total working time for the average full-time employee (40).

1.3 Tension Type Headaache

Epidemiology

TTH is the most prevalent primary headache disorder however epidemiological researches are still insufficient, especially in under-developed countries compared to migraine. GBD 2017 study estimated that there were 882.4 million new cases worldwide, roughly 63.6 million new cases in the European Union and nearly 44.5 million new cases in the USA (41). In a follow-up epidemiological study conducted in Denmark, the annual incidence of frequent TTH was determined to be 14.2 per 1,000. The incidence in women was found to be 2.6 times greater than in men. The incidence decreased with age. Among individuals aged 25 to 34, approximately 40 per 1,000 person-years were detected in women, 15 per 1,000 person-years in men, and under 5 per 1,000 person-years in both genders in the 55-64 age group (6). In a 12-24 months follow-up study conducted in adolescents aged 13-14 in Taiwan, the incidence was reported as 3.9 per 1000 person-years, and was 4.6 times greater in females than in males (42).

Although there are precise diagnostic criteria established by the International Headache Society, the estimated prevalence rates of TTH in the studies and regions highly vary because of the differences in case definitions, methodology of studies, demographics characteristics, environmental and genetic factors (2). In the 2016 GBD study, age-standardised prevalence of the prevalence of TTH was found to be 26.1% worldwide, 30.8% in women and 21.4% in men (34). In 2017, it was determined that there were nearly 2.33 billion people with TTH globally, approximately 173.7 million in the European Union (43,44). In the U.S., the prevalence rose by 31.7% from 1990 to 2017 (43). In a European study evaluating more than 33,000 Danish twins between the ages of 12 and 41, self-reported 1-year prevalence of TTH was declared to be 86% (78.9% in men and 92.5% in women), with 63.5% for infrequent episodic TTH, 21.6% for frequent episodic TTH, and 0.9% for chronic TTH (45). Data from the GBD study covering 2007 to 2017 revealed that the prevalence of TTH was 12.1%, 35.7%, and 35.8% among girls aged 5-9, 10-14, and 15-19, respectively, while for boys, the prevalence was 11.7%, 34.5%, and 34.0% in the same age groups (46).

Although the global prevalence of chronic TTH ranges from 0.2% to 4.8%, it is estimated to be nearly 2–3% in most population studies. The rates of chronic TTH prevalence vary between 3% and 3.9 for women/girls and between 1.1% and 2 % for men/boys. Chronic TTH is sparse in young adolescents (47). A large study conducted among 7900 adolescents aged 12-14 in Taiwan found a prevalence of chronic TTH of 1.0% (48).

The average age at TTH onset is 25-30 years, which is higher than that of migraine (19). The ratio of female to male for TTH is 1.2 to 1, with a much lower female preponderance than for migraine (47). The prevalence for both sexes is highest between the ages of 30 and 39, and generally diminishes with age. The prevalence varies between continents. The rate is much higher in Europe (80%) than in Asia and America (20-30%) (191). In the 2016 GBD study, the highest age-related prevalence of TTH was in Brazil and Afghanistan, while the lowest prevalence was found in China (34).

Education level has been found to be positively related with episodic TTH prevalence but inversely relationship with chronic TTH. Risk factors for TTH include being young, female gender, having poor health, difficulty relaxing after work, and getting only a few hours of sleep a night (49). A study involving adolescents in Taiwan found that frequent headaches (≥7 days per month) and female gender were related to an increased risk of chronic TTH (42). Another study identified a history of migraine, use of acute headache medications, and the severity of depression as risk factors for chronic TTH. Moreover, medication overuse was identified as a negative prognostic factor for predicting the persistence of chronic daily headache within 2 years (48). In a Danish cross-sectional headache study, poor outcome of TTH was linked to baseline chronic TTH, being unmarried, concomitant migraine, and sleep problems (49).

Depression, anxiety, and sleep disorders are more common in people with TTH compared to the general population without headaches. Anxiety and depression are related to the frequency and severity of TTH attacks. TTH is also related to other pain disorders including neck pain, low back pain, and migraine (47). 94% of patients with migraine were found to TTH, and among them, 56% experienced frequent episodic TTH (49).

Burden

Although TTH is generally considered to be less disabling than migraine, it leads to a greater socioeconomic burden on society due to its higher global prevalence. The disease burden is higher in chronic TTH patients compared to the episodic form. Globally, according to the GBD study,

TTH was identified as the second most prevalent cause of chronic disease and injury (50). The ages of 15 and 49 were the highest burdened ages in terms of YLD for TTH (47). YLD was determined as 7.1 million globally in 2017 (41). In 2019 GBD study, YLD was 4.54 million; 2.53 million for women and 2.01 million for men, accounted for 0.5% of the total YLD. It constituted 11.8% of the disease burden of all headache disorders (4).

There's relatively little information available regarding the costs associated with TTH. Results from two studies conducted in Denmark indicated that the number of workdays lost due to TTH in the population was three times greater than the number lost due to migraine (51,52). In particular, the chronic presentatipon accounts for more than 10% of the total disease absenteeism caused by any disease (19). About 8%-12% of employees with episodic TTH reported missing at least 1 day of work per year, while about 44% reported to experience decreased effectiveness days at work due to headache. For chronic TTH patients, about 12% of employees missed work days and about 47% experienced decreased effectiveness days (53). A research in U.S. estimated that only 4% of patients with TTH lost work time within a year (54). Individuals with episodic TTH reported an average of 8.9 lost workdays and 5.0 days of reduced effectiveness per person in one year, compared to 27.4 lost workdays and 20.4 days of reduced effectiveness for those with chronic TTH (55). In a clinical study examining disease burden, episodic TTH patients declared an average loss of 2.3 workdays and 1.6 household workdays over the past three months, while those with chronic TTH reported an average of 8.9 workdays and 10.3 household workdays lost (56). In a study of 1022 Brazilian university students, 24.4% of students with episodic TTH reported decrease in study performance (57).

Due to the greater prevalence of TTH and increased likelihood of many young TTH patients to seek medical advice, direct costs related to medical services and drugs are 54% greater for TTH compared to migraine. On account of the absence of a specific and efficacious treatment for TTH, individuals often consult multiple physicians and spend substantial amounts of money on various alternative treatments, often enduring much of their lives without effective pain relief for their headaches (19). The average annual cost due to episodic TTH in the 27 EU countries was estimated at €21 billion, or €303 per person. Outpatient treatment accounted for the largest part of the direct costs (€11 per person). On the other hand, indirect costs were higher than indirect costs, accounting for 92% of the financial burden. These indirect costs are associated with reduced productivity at work (€173 per person) and lost workdays (€105 per person) (58).

1.4 Cluster Headache

Epidemiology

Cluster headache, a highly debilitating headache disorder, is the most prevalent type of trigeminal autonomic cephalalgias. It is less common compared to migraine and TTH. There is little data about the epidemiology of cluster headache. The incidence ranges between 2.5 and 9.8 per 100,000-person years. It peaks in males aged 40 to 49 and in females aged 60 to 69 (19). Circannual variation in its incidence is a typical feature of cluster headache (more common in spring and autumn). Its prevalence is estimated to be between 0.1-0.5%. A meta-analysis of 16 studies determined a lifetime prevalence of 124 per 100 000 individuals and mean annual prevalence of 53 per 100 000 individuals (59).

The average age of onset ranges from 20 to 40 years, and it is more prevalent in men than in women, with a ratio of 2:1 (1). 6-8% of the patients have a family history of cluster headaches. The most prevalent patterns of inheritance are autosomal dominant followed by autosomal recessive. Episodic presentation is 6 to 25 times more prevalent than chronic presentation. Chronic cluster headache is more frequently observed in females than in males, and it is more prevalent in North America and Europe compared to Asia (60).

Suicidal thoughts were found in 55% to 64% of the patients with cluster headache and suicidal planning was in 6% of the patients in American and South Korean studies (61). Insomnia, personality disorders, and substance abuse/addiction have been shown to be associated with cluster headache, all of which can potentially influence suicidality (62). A family history, smoking, alcohol use, heavy coffee consumption, traumatic brain injury, sleep disturbance and sleep apnea syndrome are risk factors for cluster headache. The late age of onset, longer than 20 years duration for episodic form, and male gender are associated with poor prognosis (63).

Burden

Cluster headache imposes a significant burden on individuals including substantial personal impact, impaired quality of life and economic and employment-related issues. In a Danish study investigating the personal and societal burden as well as cost associated with cluster headaches in 400 patients it was reported that 94% of the patients experienced limitations in their personal and/ or occupational lives during pain attack

periods (64). Even in pain-free periods, poor/very poor health was reported 9% of episodic patients compared to only 1% of individuals without headaches. In individuals with chronic cluster headache, the likelihood of rating their health as good or very good was reported ten times lower than that of the controls and three times lower than that of patients with episodic cluster headache in remission. The average annual direct costs due to cluster headache amounted to 9,158€ for chronic form and 2,763€ for episodic form. The indirect costs associated with absenteeism from work were €11,809 per year per patient for those with chronic cluster headache and €3,558 per year per patient for those with episodic cluster headache. Moreover, during periods of attacks, 65% reduction in the productivity was estimated in the patients compared to controls. A German clinical study declared that average direct and indirect costs for an individual patient with cluster headache were €5963 over the six-month period. The costs were much higher for chronic cluster headache patients (€10,985) than for episodic patients (€258) (65).

In data from The Danish Headache Center study, 78% of the cluster headache patients declared limitations in daily life and 13% even outside of cluster periods. About 25% reported a significant decline in their ability to engage in familiy and social activities, and household chores. The absenteeism rate was found to be around 30% in the patients compared to 12% in the general population (66). A comprehensive Korean study demonstrated that cluster headache patients were less likely to be employed and often worked as freelancers or self-employed individuals compared to those suffering from migraine or TTH, as well as controls without headaches. About 85% of cluster headache patients experienced challenges at work and required sick leave, a rate that was notably higher compared to both controls with headache and without headache (67).

1.5 Conclusion

Increasing epidemiological data indicate that headache disorders particularly TTH and migraine are common worldwide. Headache disorders can have a substantial negative impact on all aspects of an individuals' lives- performance at school and work, personal relationships with family members, colleagues and friends, and and the capability to fulfill the routine daily living activities. They cause significant disability, impair quality of life and productivity, impose huge burden on both the individuls and society.

Case

A 36-year-old woman nurse presented with a 16-year history of attacks of episodic migraine. In the past medical history, the patient had depression and anxiety and was on escitalopram 10 mg daily. There was a family history of migraine in her mother and sister. She reported increase in severity and frequency of headaches over the past year. Headache attacks occured more than 15 days per month. The pain was unilateral on the right fronto-temporal area, severe, throbbing, and pulsatile. The headaches could last up to 12 hours without treatment and were accompanied by phonophobia, photophobia, nausea, and allodynia. She had acetaminophen, ibuprofen or naproxen with the average 8 tablets per week, that were not sufficiently efficacious. Sleeplessness, bright lights, stress, and noise exacerbated her headaches. The attacks were disabling; she wanted to rest and go to sleep to relieve her pain. They frequently occured at the work and affected her ability to care for the patients. She missed average 1 work day per month. Also, she reported significantly decline in the capasity to participate in social, familial, and housework activities. She was unwilling to participate in or even plans family, social, or leisure activity for because of the fear of headaches.

Comment:

This is a presentation of a patient with episodic migraine progressing to chronic form in addition to medication-overuse headache. Headache attacks disrupted her work, family and social life and caused to need high acute medications use. The quality of life of the patient diminished owing to increased frequency and intensity of headache attacks. Considerable burden imposed on the patient. She required efective individually-adjusted treatment to increase the quality of life, reduce the frequency of headache attacks and burden.

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CHAPTER 2

UNMET NEEDS IN HEADACHE

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2.1 Introduction

Headache is one of the most common painful conditions leading to disability of the affected individuals. Among all types of headaches, migraine is the condition that most frequently prompts patients to medical consulting. This disorder is the third most common disease worldwide and also the most disabling neurological disorder with distinctive clinical and pathophysiological features in the society. It causes moderate to severe disability in nearly half of the patients. The prevalence of migraine is reported to be 14-16%, meaning that one out of every seven people in the world suffers from migraine (1). In terms of age distribution, this frequency increases even further in women aged between 35-40 years (2). Because of these high rates of prevalence of migraine, unmet needs are well defined particularly in this headache condition requiring specific considerations since it poses also significant social and economic burden to the society.

Most of the migraineurs feel an extreme limitation to complete their daily activity during the headache phase and nearly one third of the patients feel similarly extremely limited in the premonitory and prodromal phase of the migraine attack (3). Disability resulting from severe headaches not only adversely affects the lives of patients and their families but also burdens society in many ways. Although there have been significant developments and innovations in this field and public awareness has been increased over the past decade, patients with headache still face several unmet needs (4,5).