PART

I

Introduction

CHAPTER
1

CHAPTER OUTLINE

Epidemiology and Quality of Life with Migraine

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INTRODUCTION

Epidemiology is defined as the study of the distribution and determinants of diseases in human populations. Thus epidemiologic studies are concerned with the extent and types of illnesses in groups of people and with the factors that influence the distribution of those diseases (Gordis, 2000). Epidemiologists investigate the interactions that may occur among the host, the agent, and the environment (the classic epidemiologic triangle) to produce a disease state. An important goal of epidemiologic studies is to identify the *etiology* of a disease, thereby enabling health-care providers to prevent or intervene in the progression of the disorder. To achieve this goal, epidemiologic studies generally proceed from studies that specify the amount and distribution of a disease within a population by person, place, and time (that is, *descriptive* epidemiology), to more focused studies of the determinants of disease in specific groups (that is, *analytic* epidemiology) (Gordis, 2000). Whether descriptive or analytic, the ultimate goal of epidemiologic investigations is prevention.

Table 1.1 summarizes some contributions of epidemiology to our understanding of the magnitude, risk factors, and impact of migraine. The application of the tools of epidemiology to headache has generated substantial methodological developments designed to collect reliable and valid information on the prevalence of headaches in nonclinical samples. With these methodologies, the high prevalence of migraine in the general population has been consistently reported, and the sex- and age-specific patterns of onset and offset of migraine have been well established. Community-based studies have also demonstrated major biases in severity and comorbidity that characterize clinical samples, particularly those obtained at tertiary referral centers for headache. Finally, epidemiologic studies have provided data on the huge impact and the personal and societal costs of migraine and other headaches.

This chapter has two major goals: (1) to summarize the magnitude and sociodemographic correlates of headache subtypes in adults and children and (2) to present

Table 1.1 Goals of Epidemiologic Studies

- Develop standardized assessments of headache subtypes
- Establish validity of diagnostic nomenclature
- Estimate magnitude of headache subtypes in the general population
- Identify risk and protective factors for headache subgroups
- Collect information on patterns of use and adequacy of treatment

information on the individual and societal impact of migraine.

MAGNITUDE OF HEADACHE SYNDROMES IN THE GENERAL POPULATION

Adults

Table 1.2 summarizes recent international population-based studies of headache and specific headache subtypes in adults. Several community studies of European samples (Jensen & Stovner, 2008) have been undertaken, and a very large American study of 15,000 households representative of the U.S. population was conducted in 1989 (Stewart et al., 1992), followed by a 10-year replication with identical methodology (Lipton et al., 2001a).

Approximately 50% of persons in the general population suffer from headaches during any given year, and more than 90% report a lifetime history of headaches (Bigal et al., 2004; Stovner et al., 2007). The average lifetime prevalence of migraine is 18%, and the estimated average past-year prevalence is 13%. Tension-type headache is more common than migraine, with approximately 52% lifetime prevalence and 22% 12-month prevalence. Approximately half of those persons who report headaches suffer from tension-type headache. Only a small minority (3%) suffer from chronic headache (Jensen & Stovner, 2008).

Children

A recent systematic review of population-based studies reported the prevalence of headache and migraine among children and adolescents during the period between 1990 and 2007 (Abu-Arafeh et al., 2010). It has been difficult to summarize the rates in these studies because many studies focus on particular age subgroups, whereas few studies have examined prevalence of headache across all years of childhood and adolescence simultaneously. The prevalence of migraine in children and adolescents is 7.7% (95% confidence interval [CI]: 7.6–7.8), and that of headaches is 58.4% (95% CI: 58.1–58.8) over a range of prevalence periods between 1 month and lifetime. Variation in the prevalence rates of migraine can be attributed to sampling differences (age, sex, and ethnic composition of the sample); methodological differences, particularly related to the method of assessment of the diagnostic criteria for headache (e.g., structured diagnostic interview, questionnaire, symptom checklist); the mode of administration of headache assessments (i.e., direct interview, telephone interview, self-reported assessment); and variation in the time frame of prevalence estimates.

The variation in estimates of childhood migraine is in part due to methodological differences, but also to the inadequacy of the current diagnostic criteria in accurately capturing migraine among youth. As demonstrated in many studies, the *International Classification of Headache Disorders—I* (ICHD-I) does not adequately distinguish the primary headache syndromes in childhood. With the publication of the *International Classification of Headache Disorders—II* (ICHD-II) in 2004, the sensitivity of diagnosis of migraine without aura in children improved from 21% to 53%, yet continued to miss almost half of all pediatric migraine (Lima et al., 2007).

Headaches in early childhood are not only difficult to classify but also continuously evolve over time (Brna et al., 2005). The likelihood of migraine at puberty is practically equal among children who present with tension-type headache or migraine at 6 years of age (Virtanen et al., 2007).

Table 1.2 Twelve-Month and Lifetime Prevalence Rates of Headache in International Population Surveys of Adults

	Prevalence Rates % [Median; (Range)]					
	12 Month			Lifetime		
Headache Subtype	M	F	Total	M	F	Total
Headaches	43 (19–69)	55 (40–83)	49 (29–77)	90 (90–93)	94 (94–99)	92 (71–96)
Migraine	8 (2–13)	16 (6–20)	13 (5–25)	13 (8–22)	23 (17–33)	18 (12–28)
Tension type	18 (13–21)	24 (23–25)	22 (18–25)	37 (32–69)	61 (37–88)	52 (35–78)

RISK FACTORS AND CORRELATES

The evidence consistently indicates that migraine is far more common in women than in men, with one-year prevalence rates ranging from 1.5% to 18.3% among women and from 0.6% to 9.5% among males (Lipton & Bigal, 2005). The sex ratio for lifetime migraine remains stable at 2–3:1 and is generally consistent across countries. The female preponderance of headaches emerges in youth, with females having a 1.5-fold greater risk of headaches and 1.7-fold greater risk of migraine than male children and adolescents.

Numerous hypotheses have been proposed to explain the gender differences in migraines. However, few studies have systematically reviewed the evidence for both artifactual and true causes of women's increased risk for migraine. Potential sources of artifactual causes of the sex difference include biases associated with sampling (i.e., increased detection of females in clinical samples), reporting (i.e., a greater tendency for women to report or be aware of migraine), definitions (i.e., diagnostic criteria more likely to cover symptoms expressed by women than men), or confounding with other factors that are more common in women (i.e., depression, anxiety, gastrointestinal syndromes).

After exclusion of possible artifactual explanations for the excess number of cases of migraine noted in women, numerous hypotheses have been considered. These include hypotheses focusing on neurobiological factors (e.g., fluctuation of reproductive hormones, increased stress reactivity in women), greater exposure or sensitivity to environmental stressors (e.g., role stress, life events associated with certain sensory stimuli), and genetic factors (e.g., greater genetic loading for migraine in women) (Low et al., 2007).

With respect to specific headache subtypes, there is a twofold greater prevalence of migraine across the lifespan in women, whereas tension-type headache affects both sexes at approximately equal rates. Sex differences among migraineurs are by no means uniform across childhood and adolescence. Whereas post-pubertal rates of migraine are significantly higher among females in almost all studies, the rates of migraine are equivalent among boys and girls younger than 12 years of age; notably, some studies even suggest a higher prevalence of migraine among boys aged 3–5 years when compared with girls of the same age group (Winner & Rothner, 2001). The American Migraine study revealed that the female-to-male gender ratio of migraine increased steadily from age 12 to about age 42, after which it declined (Stewart et al., 1991). The decline in the sex-based ratio at mid-life may correspond with the decline in estrogen levels in women as menopause approaches. This pattern also suggests that hormonal events associated with menarche may contribute to the emerging relative increases in the migraine prevalence in females in early adolescence. Headache and migraine prevalence reliably increase across the pediatric age spectrum. In the United States, frequent or severe headaches, including migraine, were reported in 4% of 4- and 5-year-olds, with the prevalence increasing to 25% in the next 10 years of childhood (Lateef et al., 2009).

Aside from sex and age, a family history of migraine is one of the most potent and consistent risk factors for migraine. Findings from twin studies implicate genetic factors as underlying approximately one-third of familial clusters of migraine, but the mode of inheritance is clearly complex. Despite an increasing number of studies examining candidate genes' association with migraine, no replicated linkage or associations between specific genes and migraine have emerged as yet, except for hemiplegic migraine. To date, the application of genome-wide association studies in cases and controls has not yielded replicated associations between migraine and genetic markers.

Migraine is strongly associated with a variety of medical disorders, especially asthma, eczema, allergies, epilepsy, cardiovascular disease, cerebrovascular disease, and particularly ischemic stroke. Anxiety and mood disorders are also strongly associated with migraine. Prospective data from community studies of youth reveal that anxiety in childhood is associated with the subsequent development of headache in young adulthood.

INCIDENCE AND COURSE OF DISEASE

Despite the large body of cross-sectional studies on the prevalence and correlates of migraine, there is a dearth of prospective research from community samples that might provide information on the incidence, stability, and course of migraine in adults. Incidence data have been reported in three prospective community surveys of adults (Breslau & Davis, 1993; Swartz et al., 2000; Lyngberg et al., 2005a) and one such study of children (Anttila et al., 2006), but the longitudinal course of specific headache subtypes in adults has been studied in only two prospective studies of community samples (Lyngberg et al., 2005a; Merikangas et al., 2011). These studies revealed that there was substantial longitudinal overlap between migraine and tension-type headache and worse long-term outcome in terms of severity and recurrence among persons with coexisting migraine

and tension-type headache (Lyngberg et al., 2005b; Merikangas et al., 2011). In contrast to the limited number of prospective studies of adults with migraine, several long-term follow-up studies of specific childhood headache subtypes have been conducted with school-based and clinical samples (Bille, 1997; Guidetti & Galli, 1998; Kienbacher et al., 2006).

The incidence of migraine is low before adolescence, but then rises rapidly until middle adulthood, and finally levels off in later life. The onset of migraine may occur in childhood, when boys and girls are equally likely to suffer from migraine. Migraine in childhood is more likely to be associated with gastrointestinal complaints, particularly episodic bouts of stomach pain, vomiting, or diarrhea, and its duration is shorter than that commonly observed in adults. In women, migraine is strongly associated with reproductive system function, with increased incidence during puberty and the first trimester of pregnancy, and is associated with exogenous hormone use. After menopause, the frequency of migraine attacks generally decreases dramatically, unless estrogen replacement therapy is administered.

The course of migraine is highly variable. Of the women in the United States who have migraine, 25% experience four or more severe attacks per month, 48% experience one to four severe attacks per month, and 38% experience one or fewer severe attacks per month. Similar frequency patterns have been observed in men (Lipton et al., 2001b). In general, both the frequency and the duration of migraine decrease at mid-life in both men and women, and the symptomatic manifestations may change substantially over time. Numerous precipitants of migraine attacks have been consistently implicated as precipitants of acute headache attacks (including hormonal changes, stress or its cessation, fasting fatigue, over-sleeping, particular foods and beverages, drug intake, chemical additives, bright light, weather changes, and exercise), but these agents/situations have been observed to vary dramatically within and between individuals in prospective research (see Chapter 4).

What happens to a child with migraine? Longitudinal population-based studies on pediatric migraine are relatively sparse. Bille (1997) reported the first extensive study of pediatric migraine epidemiology in 1962 and subsequently followed a group of children with severe migraine for 40 years. In this study, approximately 23% of these children became permanently migraine-free as adults (34% of the boys and 15% of the girls) (Bille, 1997). At the 40-year follow-up evaluation, of the initial group of migraineurs, 33% of those who had children had offspring who developed their own headaches with migrainous features. The author also showed a considerable recall bias with regard to migraine with aura: 41% of middle-aged subjects could not remember that they had aura symptoms at younger ages. This finding highlights the need for prospective follow-up studies.

Other prospective studies, utilizing ICHD-II criteria, have shown that headaches remit in 17% to 34% of subjects, persist in 20% to 48%, and transform into other types of headache in 11% to 37% (Zebenholzer et al., 2000; Camarda et al., 2002). Studies that use detailed headache diagnostic criteria suggest that as many as one-fourth of patients may evolve from migraine to tension-type headache, and vice versa (Metsahonkala et al., 1997; Zebenholzer et al., 2000; Camarda et al., 2002). In terms of prognostic factors, early age at onset (Hernandez-Latorre & Roig, 2000), psychosocial stressors (Metsahonkala et al., 1997), and psychiatric comorbidity (Guidetti & Galli, 1998) may be linked to a less favorable outcome.

IMPACT OF MIGRAINE

Individual-Level Disability

Recent community studies have underscored the enormous personal and social burden imposed by migraine in terms of both direct and indirect costs. The severity of migraine ranges from mild inconvenience to nearly total disability. More than 80% of those persons with migraine report some degree of disability. For example, data from the American Migraine Study II (Lipton et al., 2001a) revealed that more than half (53%) of migraineurs reported severe impairment in activity or the requirement for bed rest with severe headaches. The same study revealed that 92% of women and 89% of men with severe migraine had some headache-related disability, and approximately half were severely disabled or required bed rest (Lipton et al., 2001a). In addition to attack-related disability, many patients with migraine live in fear, knowing that at any time an attack could disrupt their ability to work, care for themselves or their families, or meet social obligations. Abundant evidence indicates that migraine reduces the health-related quality of life (Dahlof et al., 1997; Santanello et al., 1997). Household and family or social activities are more likely than work or school activities to be disrupted by migraine.

Some of the disability among headache sufferers can be attributed to comorbid conditions that explain a substantial proportion of the disability associated with

non-migraine severe headaches and approximately 65% of the disability associated with migraine headaches (Saunders et al., 2008). Despite the high magnitude of disability associated with migraine, only half of those individuals who suffer from debilitating migraine seek professional help.

Recurrent headaches have also been shown to have a negative impact on the quality of life in children. Children with migraine have more school absences, decreased academic performance, social stigma, and impaired ability to establish and maintain peer relationships. In a review of studies that examined the impact of headache on the functional status and quality of life of children with migraine, Kernick, Reinhold, and Campbell (2009) found substantial headache-related morbidity for a significant number of children, most notably in days lost and affected at school. On average, studies reflecting school settings found that 8% of children lost 6 days of school attendance per year. The impact of headache was directly related to headache frequency and severity of headaches. The same review also examined methodological factors in studies of headache effects in children, and recommended that future studies include control groups with standardized and validated measures of sleep impact. The quality of life in children with migraine is impaired to a degree similar to that in children with arthritis or cancer (Powers et al., 2003).

Impact of Migraine on Society

Severe headaches and migraine not only have substantial impact on the affected individual, but also have major economic implications in the form of medical expenses and employer costs (Dahlof & Solomon, 1998). The direct costs of migraine, including physician visits, emergency room visits, and prescribed and over-the-counter (OTC) medications, are estimated to exceed $17 billion to $19 billion per year (Andlin-Sobocki et al., 2005; Berg & Stovner, 2005). Indirect costs include the aggregate effects of migraine on productivity at work (paid employment), in performance of household work, and in other roles (Goldberg et al., 2005).

A recent European study of the impact of brain diseases revealed that migraine has the greatest health-care costs of all the neurologic disorders investigated, including epilepsy, multiple sclerosis, Parkinson disease, and stroke (Andlin-Sobocki et al., 2005). The bulk of the expenses attributable to migraine derive from its high population prevalence and indirect costs due to occupational disability rather than to direct health-care costs; in fact, the latter costs are lower for migraine than for the other neurologic conditions. For example, the annual U.S. direct medical costs attributable to migraine totaled an estimated $1 billion in 1999 (Lipton et al., 2001a).

During the past few years, increasing attention has been directed to the enormous public health impact of migraine. In recognition of this condition's high prevalence and burden, as well as the limited amount of research resources devoted to migraine, the World Health Organization recently launched a global campaign—known as Lifting the Burden—to reduce the burden of headache (Osterhaus et al., 1992; Stang et al., 1996; Stewart et al., 1996; Hu et al., 1999; Holmes et al., 2001).

Migraine also has a marked impact on health-care utilization. The National Ambulatory Medical Care Survey in the United States, conducted from 1976 to 1977, found that 4% of all visits to physicians' offices (more than 10 million visits per year) were for headache (National Center for Health Statistics, 1979). Migraine also results in high utilization of emergency rooms and urgent care centers (Celentano et al., 1992; Fry, 1996; Bigal et al., 2000). Vast quantities of prescription and OTC medications are taken for headache-related disorders (Celentano et al., 1992). OTC sales of pain medication in the United States (for all conditions) were estimated to amount to $3.2 billion in 1999, and headache accounted for approximately one-third of OTC analgesic use (Lipton et al., 2001a). Gross sales for triptans total approximately $1 billion per year in the United States alone (Lipton et al., 2001a).

CONCLUSIONS

Approximately 50% of persons in the general population suffer from headaches during any given year, and more than 90% report a lifetime history of headache. The average lifetime prevalence of migraine is 18%, and the estimated average past-year prevalence is 13%. Tension-type headache is more common than migraine, with a lifetime prevalence of approximately 52%, and an average 12-month prevalence of 22%. About 58% of youth suffer from headache, and the prevalence of migraine in children and adolescents is about 8%. Approximately 20% of children and adults with headache continue to suffer from headache throughout their lives, whereas 50% experience remission over extended periods.

Recent community studies have underscored the enormous personal and social burden of migraine in terms of both direct and indirect costs. These findings strongly underscore the need for research that can elucidate targets for prevention of this serious condition.

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