The Epidemiology and Impact of Migraine

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Current Neurology and Neuroscience Reports 2004, **4**:98–104
Current Science Inc. ISSN 1528–4042

Migraine is a highly prevalent headache disorder that has a substantial impact on the individual and society. In this article, we review the burden of migraine, emphasizing the population-based studies that used standardized diagnostic criteria. We highlight descriptive epidemiology, burden of disease, patterns of diagnosis, and treatment. We focus on the epidemiology and burden of probable migraine, a subtype of migraine where just one clinical feature is missing. We finish by describing approaches to improving healthcare delivery for migraine and probable migraine. Although migraine is a remarkably common cause of temporary disability, many migraineurs, even those with disabling headache, have never consulted a physician for the problem. Prevalence is highest in women, in persons between the ages of 25 and 55 years, and, at least in the United States, in individuals from low-income households. Nonetheless, prevalence is high in groups other than these high-risk groups. Probable migraine is a prevalent form of migraine, and like migraine with and without aura it produces decrements in health-related quality of life and increments in disability relative to control subjects.

Introduction

Headache is one of the most common types of recurrent pain as well as one of the most frequent symptoms in neurology [1–3]. Although almost everyone gets occasional headaches, there are well-defined headache disorders that vary in incidence, prevalence, and duration [4,5]. Headache disorders are divided into the primary and secondary forms. Secondary disorders have an identifiable underlying cause, such as an infection, a brain tumor, or stroke. In primary headache disorders, there is no apparent underlying cause [6].

Migraine is one of the most burdensome of the primary headache disorders and it continues to be misunderstood, underdiagnosed, and undertreated in clinical practice [3,5,7]. In 1989, a US population-based epidemiologic survey of migraine (the American Migraine Study I [7]), found that 16% of migraine sufferers had consulted their physician in the previous year. Ten years later, the American Migraine Study II [8••,9••] showed that consultation rates for migraine sufferers tripled (47%). However, 53% of those with migraine had not received medical care for 1 year or more, 14% had never consulted a physician for headache, and 37% had consulted in the past but had subsequently lapsed from care [9••].

Epidemiologic data helps to describe the burden of migraine as well as its scope and distribution [4,9••,10]. Understanding sociodemographic, genetic, and environmental risk factors helps identify those groups at highest risk for migraine and may provide clues to preventive strategies or disease mechanisms. Epidemiologic studies assess individuals, whether or not they seek care for their headache disorders.

In this article, we review the burden of migraine, emphasizing the population-based studies that used standardized diagnostic criteria. We highlight descriptive epidemiology, burden of disease, patterns of diagnosis, and treatment. We focus on the epidemiology and burden of probable migraine, a subtype of migraine where just one clinical feature is missing. We conclude by describing approaches to improving healthcare delivery for migraine and probable migraine.

Diagnosis and Definitions

Diagnosis is an essential prelude to conducting epidemiologic studies and measuring the burden of disease. Precise case definitions are essential to facilitate reliable and valid diagnosis. Although there is no diagnostic gold standard for the primary headache disorders, the International Headache Society (IHS) criteria provide the operational definitions that have been widely used in epidemiologic research [6,11]. According to the 2003 revision of these criteria, migraine is divided into six major categories, the two most important of which are migraine without aura (IHS 1.1) (Table 1) and migraine with aura (IHS 1.2). When just one feature required for diagnosis is missing, these patients should be classified as having probable migraine (IHS 1.6).

Table 1. International Headache Society diagnostic criteria for migraine without aura

A. At least 5 attacks fulfilling criteria B through D.
B. Headache attacks lasting 4–72 hours and occurring <15 d/mo (untreated or unsuccessfully treated)
C. Headache has at least two of the following 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 attributed to another disorder

Data from Headache classification committee of the International Headache Society [11].

Epidemiologic studies often focus on the incidence and prevalence of disease in defined populations. Incidence refers to the rate of onset of new cases of a disease in a given population over a defined period. Prevalence is defined as the proportion of a given population that has a disease over a defined period. Prevalence is determined by the product of average incidence and average duration of disease (*eg*, migraine prevalence may increase because either incidence or duration of disease is increasing). Prevalence may also be affected by demographic shifts in the population if the proportion of the population at high risk for a disease increases. For example, the aging of the population may increase the prevalence of the headache disorders most common in the elderly (*eg*, headache secondary to intracranial disease, giant cell arteritis).

The first population studies to apply the IHS criteria were conducted in Copenhagen. The population distribution of all headache disorders was examined using in-person clinical assessment in a large, representative community sample [4]. The lifetime prevalences of various headache disorders from this population are summarized in Table 2.

The Incidence of Migraine

Stewart *et al*. [12] estimated migraine incidence using reported age of onset from a prevalence study. In female subjects, the incidence of migraine with aura peaked between the ages of 12 and 13 years (14.1/1000 person-years); migraine without aura peaked between the ages of 14 and 17 years (18.9/1000 person-years). In male subjects, the incidence of migraine with aura peaked several years earlier, at around 5 years of age (6.6/1000 person-years); the peak for migraine without aura was 10.0/1000 person-years between 10 and 11 years of age. New cases of migraine were uncommon in men in their twenties. This study concluded that migraine begins earlier in male subjects than in female subjects and that migraine with aura begins earlier than does migraine without aura.

Breslau *et al*. [13], studying a random sample of young adults (aged 21 to 30 years), found that the incidence of migraine per 1000 person-years was 5.0 in male subjects and 22.0 in female subjects, similar to the incidence reported by Stewart *et al*. [12].

A study using linked medical records system showed a lower incidence [14] (probably because many people with migraine do not consult doctors or receive a medical diagnosis [15]). In this study, incidence also peaked later than in the study conducted by Stewart *et al*. [12] (because medical diagnosis may occur long after the age of onset). In this study, the average annual incidence rate per 1000 person-years was 3.4 (4.8 in women, and 1.9 in men). In women, incidence rates were low at the extremes of age and higher among those aged between 10 and 49 years, with a striking peak at the age of 20 to 29 years.

A recent study assessing the incidence of migraine in a Danish population (aged 25 to 64 years) found an annual incidence of 8.0/1000 person-years, being 15.0/1000 in males and 3.0/1000 in females. Prevalence peaked in younger women (20.0/1000 person-years) [16].

The Prevalence of Migraine

Estimates of the prevalence of migraine have varied widely according to different studies, mainly because of differences in the definition of migraine and in the characteristics of study population. In 1995, a meta-analysis of 24 studies that met inclusion criteria included only five that used IHS criteria [17]. This meta-analysis revealed that case definition, along with age and gender distribution of the study samples, explained 70% of the variation in migraine prevalence among studies. In a second meta-analysis where just studies using the IHS criteria were included, in gender-specific models (women and men were modeled separately), age and geography accounted for much of the variation in prevalence [18]. Because case definition so powerfully influences prevalence estimates, we focus on studies that used the IHS criteria for migraine.

Rasmussen [4] showed that for men, the lifetime prevalence for any kind of headache was 93%. In this study, the prevalence of migraine was 8%. For women, the lifetime prevalence was 99% for all headache and 25% for migraine. The 1-year period prevalence of migraine was 6% in men and 16% in women [4].

In the United States, the American Migraine Study I [7] collected information from 15,000 households representative of the US population. Migraine prevalence was 17.6% for women and 6% for men, which is in the same range as the estimates of Rasmussen [4]. A follow-up study, the American Migraine Study II [8••,9••], used virtually identical methodology 10 years later and demonstrated very similar prevalence estimates.

Table 2. Lifetime prevalence of primary and secondary headaches

Type	Prevalence, %
Primary	
Tension-type headache	78
Migraine	16
Secondary	
Fasting	19
Nose/sinus disease	15
Head trauma	4
Nonvascular intracranial disease (brain tumor and other disorders)	0.5

Data from Rasmussen [4].

In France, Henry *et al.* [18] reported that the prevalence of IHS migraine was 11.9% in women and 4.0% in men. A study performed in the Netherlands showed that the lifetime prevalence of migraine in women was 33% (1-year prevalence of 25%) [19]. In men, the lifetime prevalence was 13.3% and the 1-year prevalence was 7.5%. Among patients with migraine in the past year, 63.9% had migraine without aura, 17.9% had migraine with aura, and 13.1% had migraine both with and without aura. Migraineurs suffered a median of 12 migraine attacks per year; 25% had at least two attacks per month [19].

In England, a recent study showed that 7.6% of men and 18.3% of women reported migraine with or without aura within the past year [20]. Prevalence of migraine varied with age, rising through early adult life and declining in the late forties and early fifties. Prevalence was higher in whites than in other ethnic groups. If these findings in mainland England are projected to the entire population of the United Kingdom, the authors estimated that 5.85 million people aged 16 to 65 years experience 190,000 migraine attacks every day and lose 25 million days from work or school each year because of them.

A number of other studies in Western Europe, Asia, and Africa have recently examined the prevalence of migraine [21–24].

Age and Sex Influence Migraine Prevalence

Sociodemographic variables, including age, gender, education, income, and geography, influence migraine prevalence. Before puberty, migraine prevalence is higher in boys than in girls; however, as adolescence approaches, incidence and prevalence increase more rapidly in girls than in boys [25–28]. A meta-analytic summary of prevalence studies shows that prevalence increases throughout childhood and early adult life until approximately the age of 40 years, after which it declines (Fig. 1) [3]. The gap between peak incidence in adolescence and peak prevalence in middle-age indicates that migraine is a condition of long duration.

The female to male migraine prevalence ratio also varies with age [3]. The onset of hormonal changes associated with menses may contribute to this variation [29]. However, hormonal factors cannot be the sole cause; differences persist to age 70 years and beyond, well beyond the time that cyclical hormonal changes can be considered a factor [29].

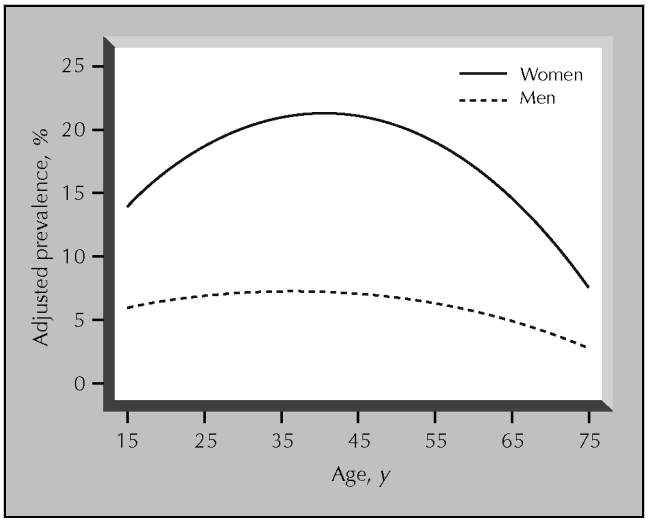

Figure 1. Adjusted prevalence of migraine by age from a meta-analysis of studies using International Headache Society criteria. (*Adapted from* Scher *et al.* [3].)

Socioeconomic Status May Influence Migraine Prevalence

The relationship between migraine prevalence and socioeconomic status is uncertain. In his studies of children, Bille [25,26] did not find an association between migraine prevalence and intelligence. Similarly, in adults, epidemiologic studies do not support a relationship between occupation and migraine prevalence [30]. However, in both the American Migraine Study I and II, migraine prevalence was inversely related to household income (*ie*, migraine prevalence fell as household income increased) [7,8••,9••]. This inverse relationship between migraine and socioeconomic status was confirmed in another US study based on members of a managed care organization [31] and in the National Health Interview Study [32]. In the latter study, migraine prevalence was highest in low-income groups; prevalence was lowest for middle-income groups and began to rise in the high- income group. In Europe, although the Genetic Epidemiology of Migraine (GEM) study [19] failed to demonstrate an association between migraine and socioeconomic status, a recent study in England showed this relationship [20].

The higher prevalence in the lower socioeconomic groups may be a consequence of a circumstance associated with low income and migraine, such as poor diet, poor medical care, or stress [3]. It may also reflect social selection; that is, migraineurs may have lower incomes because migraine interferes with educational and occupational function, causing a loss of income or the ability to rise

from a low-income group. The relationship of migraine and socioeconomic status requires further study.

Ethnicity and Geography Influence Migraine Prevalence

Migraine prevalence also varies by ethnicity and by geographic region. In the United States, it is highest in whites, intermediate in blacks, and lowest in Asians [3]. Similarly, a meta-analysis of prevalence studies suggests that migraine is most common in North and South America, as well as Europe, but lower in Africa, and often lowest in studies from Asia [3]. The influence of reporting bias on these findings cannot be excluded. However, the data do suggest that ethnicity-related differences in genetic risk may contribute.

The Co-morbidity of Migraine

The term "co-morbidity" is used to refer to the greater than coincidental association of two conditions in the same individual [33]. Migraine is co-morbid to several disorders, including epilepsy, depression and anxiety disorders, and stroke [34]. A recent population study showed that, compared with nonmigraineurs, significantly more migraineurs had asthma (odds ratio of 1.6; 95% CI, 1.1 to 2.4) or chronic musculoskeletal pain (odds ratio of 1.7; 95% CI, 1.5 to 2.1) [19]. Understanding the co-morbidity of migraine is important from a number of different perspectives [34]. First, co-morbidity has implications for diagnosis. Migraine overlaps in symptom profile with several of the conditions comorbid with it. For example, both migraine and epilepsy can cause transient alterations of consciousness as well as headache. Second, when two conditions are co-morbid, the presence of migraine should increase the index of suspicion for the other. Third, co-morbid conditions may impose therapeutic limitations but may also create therapeutic opportunities. For example, an antidepressant may be the first choice to treat migraine and depression. Finally, the presence of co-morbidity may lead to overestimates of the burden of disease. Migraine sufferers may utilize healthcare resources not just because of migraine, but because of co-morbid depression.

The Impact of Migraine on the Individual

The burden of migraine is significant both to the individual sufferer and to society [7,8••,9••,18,35]. Within the United States, the American Migraine Study II estimates that 28 million US residents had severe migraine headaches in 1999 [9••]. Nearly one in four US households has someone who suffers from migraine. Twenty-five percent of women in the United States who have migraine experience four or more severe attacks a month; 35% experience one to four severe attacks a month; 38% experience one, or less than one, severe attack a month. Similar frequency patterns were observed for men. In the American Migraine Study II, 92% of women and 89% of men with severe migraine had some headache-related disability [9••]. About half were severely disabled or needed bed rest. In addition to the attack-related disability, many migraineurs live in fear, knowing that at any time an attack could disrupt their ability to work, care for their families, or meet social obligations. Abundant evidence indicates that migraine reduces health-related quality of life.

The Family Impact of Migraine

The impact of migraine extends to household partners and other family members. In a recent study, one half of the participants believed that because of their migraine they were more likely to argue with their partners (50%) and children (52%), whereas majorities (52% to 73%) reported other adverse consequences for their relationships with their partner and children and also at work. A third (36%) believed they would be better partners but for their headaches. Participating partners partly confirmed these findings: 29% felt that arguments were more common because of headaches and 20% to 60% reported other negative effects on relationships at home. Compared with subjects who did not have migraine regarding their work performance, a statistically significantly higher proportion of migraine partners were unsatisfied with work demands placed on them (P=0.02), with their level or responsibilities and duties (P=0.02), and with their ability to perform (P=0.001) [36].

Societal Impact of Migraine

Migraine has an enormous impact on society. Studies have evaluated both the indirect costs of migraine as well as the direct costs [35,37,38]. Indirect costs include the aggregate effects of migraine on productivity at work (paid employment), on household work, and in other roles. The largest component of indirect costs is the productivity losses caused by absenteeism and reduced productivity while at work. Hu *et al.* [35] estimated that productivity losses due to migraine cost American employers 13 billion dollars per year. A European study estimated that 5.7 working days were lost per year for every working or student migraineur (although the most disabled 10% of migraineurs accounted for 85% of the total), which projects to a loss of 25 million days from work or school each year in England [20].

Migraine's impact on healthcare utilization is marked as well. The National Ambulatory Medical Care Survey [39], conducted from 1976 to 1977, found that 4% of all visits to physicians' offices (over 10 million visits a year) were for headache. Migraine also results in major utilization of emergency rooms and urgent care centers [40]. Vast amounts of prescription and over-the-counter (OTC) medications are taken for headache disorders. OTC sales of pain medication (for all conditions) were estimated to be

3.2 billion dollars in 1999 in the United States, and headache accounts for about one third of OTC analgesic use [41]. Gross sales for the triptans are about 1 billion dollars per year in the United States.

Migraine is a lifelong disorder. Bille [25,26] followed a cohort of children with severe migraine for up to 37 years. As young adults, 62% were migraine-free for more than 2 years, but only 40% continued to be migraine-free after 30 years, suggesting that migraine is often a lifelong disorder. For 15 years, Fry [40] collected information on migraine patients in his general practice in Kent, England. His data showed a tendency for the severity and frequency of attacks to decrease as the patients got older. After 15 years, 32% of the men and 42% of the women no longer had migraine attacks. Waters [30] noted a similar decrease in migraine prevalence.

The Prevalence and Impact of Probable Migraine

Most epidemiologic studies focus on the two common forms of migraine: migraine without aura (IHS 1.1) and migraine with aura (IHS 1.2). Clinic-based and some population-based studies show that a large number of patients with migrainous features fail to fully meet the IHS criteria for these two types of migraine [42,43]. These patients often fulfill all criteria but one for migraine with or without aura. This condition is termed "probable migraine" (PM) in the IHS classification, replacing the old term "migrainous disorder." Estimates of the prevalence of PM vary widely. A population-based study assessing 4000 men and women aged 40 years using the IHS criteria found that the lifetime prevalence of PM was 2.5%, with a female to male ratio of 1.2:1 [42]. Prevalence for a period of 1 year in the American Migraine Study II was similar (2.6% for men, 6.3% for women) [9••]. In a French population study, Henry *et al.* [18] screened 10,585 subjects aged 15 years and older and found a standardized prevalence for migraine (IHS categories 1.1 and 1.2) of 7.9% (11.2% for women and 4.0% for men) and for PM (IHS category 1.6) of 9.1%. In this study, PM was more prevalent than migraine with or without aura. The impact of PM is poorly understood.

We recently conducted a study assessing the prevalence and impact of PM within a health plan (Lipton, Unpublished data). Among 8579 respondents, the 1-year prevalence for migraine with and without aura (strict migraine) was 14.7% (19.2% in women and 6.6% in men); for PM it was 14.5% (19.6% in women, 13.1% in men). Pooling strict migraine and PM, the prevalence of all migraine was 29.2% (38.8% in women and 19.6% in men). The prevalence of strict migraine and PM was higher in women, whites, and in early middle-age relative to control subjects. Health-related quality of life was reduced in the PM, strict migraine, and all-migraine groups compared with control subjects (mental health scores, respectively, of 50.2, 48.2, 50.9, and 53.1; $P<0.0001$; and physical health scores, respectively, of 46.8, 48.8, 47.8, and 51.2; $P<0.0001$). The proportion of subjects with high disability relative to control subjects was elevated in PM, strict migraine, and all migraine groups (Migraine Disability Assessment [MIDAS] III and IV scores of 13%, 31%, 22%, and 3.7%, respectively; $P<0.0001$). Strict migraine and PM were associated with an increased risk of depression.

Diagnosis of this large group of headache sufferers is an important issue in clinical practice. Given the overlap of symptom features, the profile of familial aggregation, and treatment response profiles, it is likely that PM involves the same pathophysiologic process as those with IHS strict migraine.

Managing the Burden of Migraine

Measuring the burden of migraine should be a prelude to effective treatment designed to reduce that burden. A number of long-term studies have examined the impact of migraine and benefits of treatment on workplace and nonworkplace productivity [44]. Sumatriptan was demonstrated to reduce migraine-associated productivity loss during a minimum 8-hour work shift by approximately 50% compared with placebo, alleviating headache in more than 75% of subjects in the workplace [45]. A prospective, sequential, multinational (five countries) study evaluated the effects of subcutaneous sumatriptan on health-related quality of life [46]. Scores on all questionnaire domains were significantly improved after 12 weeks (in all countries) and 24 weeks (in four of five countries) of sumatriptan therapy compared with 12 weeks of usual therapy. Rizatriptan was also more efficacious than placebo in improving the functional disability [47]. Similar studies performed with other triptans also highlight that acute treatment improves health-related quality of life, although benefits develop over months.

Reducing the burden of migraine requires appropriate diagnosis. A recently developed three-item screen identifies migraine in the primary care setting with good sensitivity (0.81), specificity (0.75), and positive predictive value (0.93) [48]. Using this screener should help in improving the recognition of migraine. In individuals who screen positive, once the diagnosis of migraine is confirmed, disability should be assessed.

Figure 2 provides a schematic view of how screening and assessing disability may be used to provide appropriate treatment in accordance with the US Headache Consortium Guidelines [49]. We propose assessing the disability with the MIDAS questionnaire. Simple analgesics are appropriate for first-line acute treatments for these patients with low MIDAS scores (grades I or II). If simple analgesics are unsuccessful, various combination treatments (*eg*, aspirin plus metoclopramide) may be needed. If these treatments fail, further escalation may be necessary. A MIDAS score of 11 or over (grade III/IV) indicates high medical need. Specific acute therapies, such as the 5-$HT_{1B/1D}$ receptor agonists,

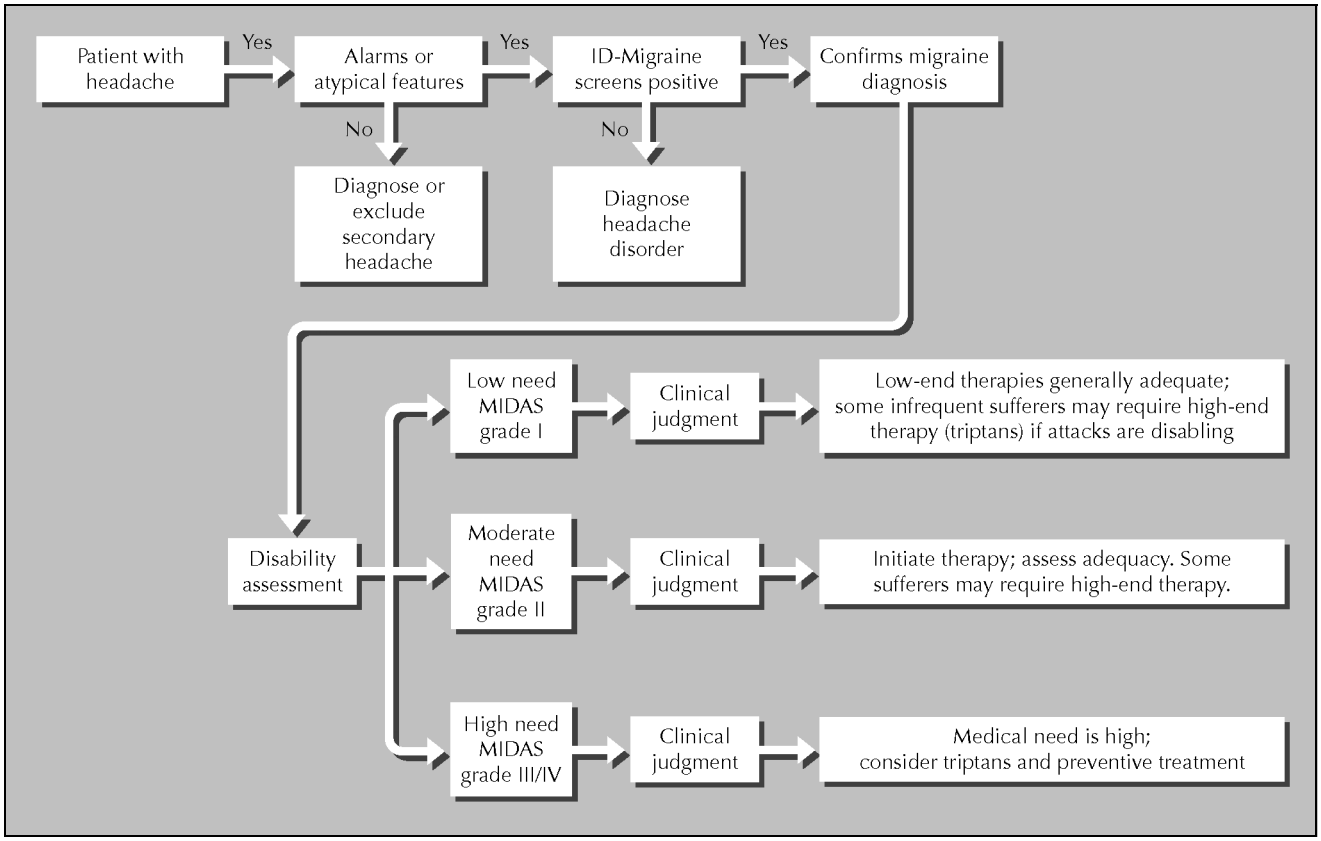

Figure 2. The disability-based approach to the management of migraine. (MIDAS— Migraine Disability Assessment.) (*Adapted from* Matchar *et al*. [49].)

may be needed by these patients, together with prophylaxis where necessary. Of course, any specific sequence of treatment recommendation requires empirical testing.

Conclusions

Using the IHS criteria, large, population-based epidemiologic studies from most regions of the world have shed light on the descriptive epidemiology and burden of headache. Although migraine is a remarkably common cause of temporary disability, many migraineurs, even those with disabling headache, have never consulted a physician for the problem. Prevalence is highest in women, in persons between the ages of 25 and 55 years, and, at least in the United States, in individuals from low-income households. Nonetheless, prevalence is high in groups other than these high-risk groups. PM is a prevalent form of migraine, and like migraine with and without aura it produces decrements in health-related quality of life and increments in disability relative to control subjects.

Acknowledgments

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