

Chapter

1

Epidemiology of the psychiatric comorbidities of headache

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“Comorbidity” refers to the occurrence of two conditions in the same individual at a frequency greater than would be expected by chance. [1] Migraine is comorbid with a number of medical, neurologic, and psychiatric disorders. Examples of medical comorbidities include asthma, [2] coronary heart disease, [3] and chronic pain disorders. [4–7] Neurologic comorbidities include stroke and epilepsy, [8] and psychiatric comorbidities include anxiety, depression, panic disorder, and bipolar disorder. [9,10,]

Comorbidities are best studied in representative samples because the prevalence of disease and the association among disorders is sometimes altered in clinic-based samples. This phenomenon, known as Berkson bias, can lead to under-estimates or over-estimates of the rates of co-occurrence for various disorders. Berkson bias arises when patterns of symptoms influence patterns of care seeking for a range of medical disorders. For example, someone with migraine and depression may be more likely to seek medical care with complaints of head pain and sadness than someone who experiences only one of these disorders. Clinic-based studies of comorbidities are useful for generating hypotheses about comorbidities and for characterizing patient groups. They cannot be relied upon to determine if two conditions are actually occurring together with frequency greater than chance.

Both clinic and population studies suggest that migraine is comorbid with a number of psychiatric disorders including depression, [11,12] anxiety [11,13,14] posttraumatic stress disorder, [15] chronic pain, [6] fibromyalgia, [16] and other medical disorders such as asthma. [2] In addition, rates of a number of comorbid conditions increase with the frequency of migraine attacks, and are higher for episodic migraine (EM) than for chronic migraine (CM). In the American

Prevalence and Prevention (AMPP) study, persons with CM ($n = 655$) are about twice as likely than persons with EM (11,249) to have depression, anxiety, and various chronic pain disorders. [2] Respiratory disorders including asthma, bronchitis, and COPD, and cardiac risk factors including hypertension, diabetes, high cholesterol, and obesity are significantly more likely to be reported by those with CM.

The broad range of comorbidities associated with headache, and the increasing risk of comorbidity with headache frequency, have important implications for healthcare professionals. Research indicates comorbidities negatively impact headache-related disability and health-related quality-of-life, further justifying an enhanced understanding of co-existing conditions to inform clinical practice.

This chapter focuses on the psychiatric comorbidities of migraine and other headache disorders. The nature of epidemiologic research, the importance in differentiating between population and clinic-based studies, the clinical relevance of comorbidity, and the potential mechanisms that link migraine to its psychiatric comorbidities are discussed. Several key studies are examined as to what they reveal about psychiatric comorbidities and headache disorders.

Epidemiology

Epidemiology is the study of the distribution and determinants of health-related states or events in human populations and its application to the prevention and control of health problems. [17,18] Broadly, epidemiologists focus on populations and the collective health of a community, whereas clinicians focus on the health of individual patients assessed one at a time. The

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population focus makes it easier to study risk factors and protective factors for illness. The developmental perspective includes understanding the natural history of a condition within a population, over time, as well as over the lifespan of an individual. The developmental perspective takes into account the rate of onset or incidence of a condition and the average duration of a condition as well as its natural progression.

Epidemiology not only involves the study of the distribution of health-related states or events in human populations; epidemiologists also provide data for directing public health action. [19] Results of epidemiologic studies can provide public health officials with information about who is at greatest risk for disease, where the disease is most common, when the disease occurs most frequently, and what public health programs might be most effective. This information can then lead to more efficient resource allocation and programs designed to educate, prevent, and control disease spread. The results of epidemiologic studies provide a wealth of information that goes beyond the individual patient at a particular point in time to provide a more comprehensive understanding of disease processes.

Epidemiologists use a variety of study designs to identify the distribution, determinants, and natural history of disorders in populations. Cross-sectional studies are often performed to document disease prevalence, or the number of people afflicted with a given disease at a single point in time. [20] Although these studies provide insight into communities at risk, they do not illuminate etiology. Cross-sectional studies are useful for documenting comorbidity, but leave many questions unanswered. Case-controlled studies identify persons with the disorder (cases) and persons without (controls) and attempt to elucidate exposures that precede the onset of the disease. These exposures can include environmental or genetic factors or the occurrence of a comorbid disorder. This study design is particularly useful in studying rare diseases and serves as a good first step in trying to identify a cause/effect relationship. If the identified cases have headaches, the case control design can determine if a comorbid condition is associated with an increased rate of migraine onset but not the converse. The principal limitation of the case control design is recall bias.

Prospective or cohort studies measure host and environmental factors at a time zero and then follow subjects over time to elucidate factors which predict onset of disease. Temporal relationships can be established and confounders can be more easily controlled.

However, prospective studies are more costly and, due to a long follow-up period, more sensitive to subject attrition. [18] If the cohort includes persons with and without migraine, the rate of disease onset in persons with migraine can be determined. To establish a bidirectional relationship, both persons with migraine and the comorbidity need to be sampled in order to determine the rate of onset of each disorder in those who have the other disorder.

Once a relationship is demonstrated, experimental research (i.e., randomized clinical and preventative trials) may be useful. For the study of comorbidity itself, randomized trials are not possible. One can assess the influence of the comorbidity on prognosis and determine if treating migraine improves the outcomes for the comorbid disorder, and if treating the comorbid disorder improves migraine outcomes. The experimental design allows investigators to measure the effect of a manipulated independent variable on outcome measures. For study accuracy, attention must be paid to standardization, replicability, and control. [21] Most clinical trials have a control group, which does not receive the experimental treatment, randomization in which the subjects are assigned to control or treatment group without bias, and blinding of the examiners to the status of each participant as experimental or control subject.

Methodological issues may limit studies. It is imperative, when investigating a possible diagnostic relationship, that consistent diagnostic criteria be established and utilized reliably. Unfortunately, a great portion of the studies done to investigate migraine comorbidities were performed prior to the establishment of the International Headache Society Criteria, which limits their validity. Studies must be adequately powered and bias must be limited. The ideal study for investigating a potential comorbid relationship is a bidirectional, population-based study of incidence, where a population that has only migraine is followed over time to assess whether or not they develop a second diagnosis. Concurrently, a sample with a diagnosis of interest is followed over time to see if they develop migraine.

Psychiatric comorbidities in headache

Several large-scale population-based studies have confirmed clinicians' longstanding suspicions: depressive and anxiety disorders are more prevalent in patients with headache. [22] Thus far, clear associations have

been established between migraine and Major Depression, anxiety disorders, posttraumatic stress disorder (PTSD), substance abuse, bipolar disorder, suicide attempts, and childhood maltreatment and abuse. [23] Much research involving migraine and mood disorders, including numerous prospective, large-scale, population-based studies, have focused on depression. Population-based studies examining the prevalence of depression in migraine patients report ranges from 3.8% to 57.0% compared with the general population lifetimes', rates of 16%. [13, 24–27]

Additionally, anxiety disorders have been found to be significantly associated with migraine in both clinical and community-based studies. When anxiety disorders are further broken down into Generalized Anxiety Disorder and Panic Disorder, both conditions are found independently to have a higher prevalence in patients that suffer from migraines. A population-based study done by Breslau *et al.* in 1991 finds that anxiety disorder is almost twice as likely to be diagnosed in migraineurs than in the general population (> 50% vs. 27% of the general population). [22] A three-fold increase in migraine prevalence in patients with bipolar spectrum disorders has been demonstrated. [28]

Tension-type headache frequently is complicated by comorbid psychiatric conditions as well. Rates of depression and anxiety disorders are significantly higher in this group than in the general population. [29] Other comorbid conditions may include personality disorders and bipolar disorder. However, the rates of these disorders among tension headache patients have not been as well studied. [30]

Chronic daily headache, defined as headache experienced 15 or more days a month, [31] has been associated with higher levels of anxiety and depressive disorders as well. [26] A clinic-based study performed by Juang *et al.* demonstrates that major depression and panic disorders are highly prevalent in patients with tension-type headache and migraine and that these associations are greater when the headaches are transformed to chronic. [13,32]

Patients with migraine and tension-type headache exhibit psychiatric illnesses at a disproportionately higher rate than individuals with no history of recurrent headache. [33,34] These comorbid relationships have been identified in epidemiological research as well as in clinical studies of treatment-seeking patients. [35] Other chapters of this book will outline further distinct psychiatric diagnoses and their relationship to the varying headache types in further detail.

Understanding the mechanisms of comorbidity

Several theories explain why two conditions appear to be associated. [36] Sometimes, the association may be a consequence of methodologic artifact such as Berkson bias as discussed above. If symptom features overlap, diagnostic confusion may lead to spurious associations. Sometimes there may be a unidirectional causal link, implying that the presence of one condition predisposes to another. [37] Shared environmental or genetic risk factors may account for the comorbidity. An underlying brain state may arise as a consequence of genetic or environmental factors and predisposes to the comorbid disorders. [36] (See Fig. 1.1.) For example, migraine and epilepsy have been found to be comorbid and both conditions can involve a transient altered level of consciousness. Additionally, transient ischemic attacks and migraine with aura both involve reversible focal neurologic deficits and these conditions have also been found to be comorbid.

Unidirectional causal models suggest that an index disease increases the risk of the comorbid disorder. The relationship between disorders, such as migraine and depression, may be unidirectional or bidirectional. As noted above, for migraine and depression, the association is bidirectional. Breslau and colleagues [38] assess the headache and depression status of 1007 young adults via interview using 1988 International Headache Society (IHS) criteria and NIMHS-DIS, respectively. Three and a half years later, 979 participants are re-interviewed. Persons with migraine (vs. those without) stand a greater risk for major depression (relative risk [RR], 3.2; 95% CI, 2.3–4.6). In addition, persons with major depression (vs. those without) stand a greater risk for migraine (RR, 3.1; (95% CI, 2.0–5.0). [38]

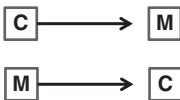
Breslau and colleagues [39] investigate the incidence of new-onset migraine as a function of baseline depression (and vice versa) during a 2-year follow-up period. At baseline, subjects are screened for depression and migraine and fall into one of the following headache groups: Migraine ($n = 496$), Severe headache ($n = 151$), or No history of severe headache ($n = 539$). The lifetime prevalence of depression at baseline is 42.1%, 35.8%, and 16.0% for the Migraine group, Severe headache group, and No history of severe headache group, respectively. In addition, analyses show that the incidence of new-onset depression is 10.5%, 5.1%, and 2.0% in the Migraine, Severe headache, and No history of severe headache groups, respectively. Further supporting the

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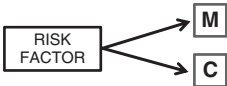
1. Comorbidity may arise by coincidence or selection bias (spurious association).



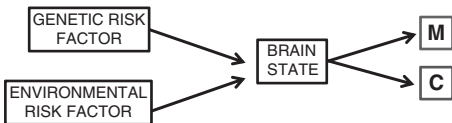
2. One condition may cause the other (unidirectional causal models).



3. The conditions may be related due to shared environmental or genetic risk factors.



4. Environmental or genetic risk factors may produce a brain state that gives rise to both conditions.



* M = migraine, C = comorbid condition

Fig. 1.1. Potential sources of comorbidity.

bidirectional causal model of comorbidity, the incidence of new-onset migraine is 9.3% in control subjects with a history of depression and 2.9% in controls without. No significant associations are found in either direction between other types of severe headache and major depression.

Shared environmental or genetic risk factors represent another possible explanation for the phenomenon of comorbidity. Merikangas and colleagues find a greater incidence of migraine in the relatives of probands with migraine (21%) vs. the relatives of persons without migraine (10%). In parallel, investigators find a greater incidence of depression in relatives of probands with depression (22%) vs. the relatives of persons without depression (10%). Given that little cross-transmission of migraine and depression between probands and relatives is found, these comorbidities may be due to non-genetic factors that aggregate within families. Therefore, investigators suggest that depression might be a pathological condition resulting from migraine or the diathesis, which results in both depression and migraine. [40]

In a separate longitudinal study, Merikangas and colleagues demonstrate a familial association between migraine and affective/anxiety disorders, although the rates of anxiety and depression are elevated only in conjunction with migraine (OR, 2.3; 95% CI, 1.29–4.0), indicating a syndromic relationship between migraine

and affective/anxiety disorders. [28] Environmental and genetic risk factors may produce a latent brain state that precipitates co-existing conditions; that is, conditions share a pathophysiologic mechanism. For example, cortical excitability is seen in both migraine and epilepsy. Regarding migraine and mood disorders specifically, Burstein *et al.* propose that several brain areas, including the hypothalamic, limbic, and cortical regions, are activated during migraine. [41] Pain signals are conveyed through trigeminovascular projections to areas of the brain that are competent to produce migraine symptoms as well as depression. Consistent with this hypothesis, some researchers speculate that serotonergic and dopaminergic dysfunction underlies the comorbidity of depression and migraine. [42,43,44] Because altered levels of serotonin are often observed during migraine attacks, migraines are frequently treated with selective serotonin agonists (i.e., triptans). Experimental evidence suggests that persons with anxiety and persons with migraine have a polymorphism in the 5-HT transporter gene. [45] The established relationship between depression/anxiety and serotonergic dysfunction warrants speculation that the source of migraine and mood/anxiety disorder comorbidity is aberrant serotonin signaling. Moreover, migraine is often accompanied by dopaminergic symptoms such as nausea and vomiting. Experimental data reveal higher levels of dopamine

receptors on peripheral lymphocytes of persons with migraine relative to controls, indicating a hypodopaminergic state in migraineurs. The link between dopamine deficiency and depression is equally well established. Thus, reduced dopamine levels may contribute to the comorbidity of depression and migraine.

Both migraine and depression may be mediated by the cascade of neuronal events associated with central sensitization and its clinical marker, allodynia. [46] Cutaneous allodynia (CA) is indicative of central sensitization, a state in which abnormally excited neurons cause a reduced pain threshold and hypersensitivity to noxious and innocuous stimuli alike. Lending additional support to the latent brain state model of comorbidity is the discovery that migraineurs with major depression (vs. those without depression) experience worse cutaneous allodynia (CA). Bigal and colleagues analyze data from 16 573 study participants with “severe headache” who completed the Allodynia Symptom Checklist (ASC-12) and the PHQ-9 for depression. The incidence of CA (as determined by ASC score ≥ 3) is 68.3% in persons with CM, compared with 63.2% in persons with EM ($P < 0.01$). Severe CA, (ASC score ≥ 9), was highest among persons with CM (28.5%) compared to those with EM (20.4%). In all persons with headache, regardless of type, the CA severity is highest among respondents who are depressed, with CM respondents having the highest ASC-12 sum scores. In adjusted analyses, depression has an incremental influence on the prevalence of CA. Compared to persons with no depression, persons with mild depression have a prevalence ratio (PR) of 1.22 (95% CI, 1.10–1.35). Persons with moderate depression and moderately severe depression are also more likely to have CA compared to those without depression (PR, 1.4; 95% CI, 1.23–1.58 and PR, 1.51; 95% CI, 1.34–1.96, respectively). The PR for CA is highest in those with severe depression (PR, 1.62; 95% CI, 1.34–1.96). [47]

The psychiatric comorbidities of headache are clinically important

Understanding the psychiatric comorbidities of headache is important for many reasons. [36,48] These comorbidities, particularly depression and anxiety, are extremely common in persons with migraine and have implications for diagnosis, treatment and our understanding of disease mechanisms. When conditions are comorbid, the usual principle of diagnostic parsimony (find a single unifying diagnosis that accounts for the

patient’s signs and symptoms) does not apply. Once a diagnosis of migraine has been established, it becomes more likely that psychiatric comorbidities are present, warranting a heightened index of suspicion.

The existence of comorbidities also has implications for treatment, creating opportunities and imposing limitations. Treatment choices should be informed by comorbid conditions. For example, treatment with a tricyclic antidepressant may benefit both disorders in a patient with migraine and depression, though undertreatment of depression is possible. Conversely, a known comorbid condition may impose therapeutic limitations. For example, depression is viewed as a relative contraindication for the use of beta-blockers in migraine.

Efforts to understand these relationships are informed by the directionality of association. In 1994, Breslau and colleagues demonstrate that there is a bidirectional relationship between depression and migraine, with each condition increasing the incidence of the other. [38] These bidirectional relationships challenge simple unidirectional causal models. For example, migraine is unlikely to be just a somatic manifestation of depression because migraine onset may precede depression onset. Conversely, depression is unlikely to be a consequence of recurrent episodes of unpredictable pain, a form of learned helplessness, because depression may precede migraine onset. The complexity is illustrated by a small, open-label pilot study showing that a treatment that reduces headache frequency without acting on the central nervous system (onabotulinum toxin A), also relieved depressive and anxious symptomology. [49] These findings further emphasize the need to recognize an underlying psychiatric condition prior to developing a treatment plan. Once comorbidity and its directionality are established, further investigations can clarify the shared pathophysiology of the disorders.

Comorbidities may also influence the clinical course and prognosis of migraine, potentially leading to increased migraine-related disability and impact, diminished health-related quality of life, and poor treatment outcomes. Psychiatric comorbidities can influence the frequency and severity of migraine, and impact disease prognosis, treatment, and clinical outcomes. [50,51] Some psychiatric comorbidities, including depression and anxiety, have been associated with increasing migraine attack frequency, or progression from episodic to chronic migraine. [12,14] Migraine can be conceptualized as a chronic disorder with episodic manifestations. [52] The clinical course is variable. Patients with migraine may remit spontaneously

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for unknown reasons, they may continue to have intermittent attacks for many decades, or they may develop a clinically progressive disorder characterized by attacks of increasing frequency at times leading to headaches on more days than not. Episodic migraine (EM) is defined as meeting ICHD-2 criteria for migraine with an average of 14 or fewer headache days per month. Chronic migraine (CM) is defined as headache on 15 or more days per month for at least 3 months. The process of developing CM from EM, sometimes termed “transformation” or “progression,” occurs in approximately 2.5% of persons with EM annually. [53] Transformation is associated with various modifiable (e.g., medication overuse, BMI) and unmodifiable (e.g., traumatic brain injury) risk factors. Depression and anxiety may be modifiable risk factors for migraine progression. [12,14] Chronic migraine is associated with more substantial disability than episodic migraine in multiple ways. [54] Additionally, psychiatric conditions often affect the coping mechanisms of migraine patients, thereby increasing headache-related disability, reducing quality of life, and often making them more difficult to treat. [55] Jette *et al.* demonstrates in a population-based study that migraine in association with various mental health disorders results in poorer health-related outcomes compared with migraine or with a psychiatric condition alone. [56]

The occurrence of comorbidities may provide clues to mechanisms underlying disease based on environmental or genetic risk factors common to migraine and its coexisting conditions. Further investigations may clarify these mechanisms. For example, it is likely that the co-occurrence of depression and anxiety with migraine may reflect neurochemical alterations common to these disorders.

Conclusion

Headaches are comorbid with many psychiatric disorders including depression and anxiety. Rates of psychiatric comorbidity are even higher among persons with more frequent headache (i.e., CM). Although this elevated rate is confirmed in both population and clinic studies, it remains important to discriminate between these samples as they differ in significant ways. In addition, evidence indicates that co-existing conditions are associated with worse treatment outcomes, increased headache-related disability, and reduced health-related-quality-of-life, further underscoring the need to study and understand comorbidity.

The diagnosis, prognosis, and treatment of migraine are confounded by comorbid psychiatric disorders. The high rates of psychiatric comorbidity with migraine highlights the importance for health-care professionals (HCPs) to maintain diagnostic vigilance and provide appropriate treatment or referrals when necessary. When comorbid psychiatric disorders are present, it is important to take all disorders into account in formulating a treatment plan and remain mindful of the negative impact that psychiatric disorders can place on treatment outcomes, adherence, and general quality of life. [57–59] Buse, Andrasik, and Sollars [60] and Maizels, Smitherman, and Penzien [61] review and provide suggestions in screening for psychiatric comorbidity among persons with headache.

Many theories exist to explain the associations. These include models of causal link, shared environmental and genetic factors, and latent brain state. Nonetheless, many questions remain unanswered. Additional research is needed to increase our understanding of these relationships and subsequently, to enhance our knowledge of the pathophysiology, directionality, and treatment of both headaches as well as their comorbid psychiatric conditions.

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Migraine

Mark W. Green

“Migraine” is a diagnosis used broadly by headache specialists to describe a phenotype, undoubtedly influenced by many genotypes yet to be identified. The main feature in common among these phenotypes is a low threshold for the development of headache among migraineurs. The International Classification of Headache Disorders, 2nd Edition (ICHD-2) [1] definitions for migraine are far more specific.

Background

The term “migraine” is a derivation of Galen’s *hemicrania* that described a paroxymal disorder of severe hemicranial pain, vomiting, and photophobia often relieved by darkness and sleep. Hemicrania was corrupted into low Latin as *hemigranea* and *migranea* and eventually became *migraine*. However, the term led many practitioners to assume that migraine had to be associated with unilateral head pain; in fact it is commonly bilateral. When the condition is mild, many with this distribution come to be diagnosed as having *tension headache*.

Diagnosis and clinical features

Although many variations exist, migraine is typically a recurring headache syndrome associated with other neurological symptoms, frequent symptom-free intervals, and is commonly provoked by stereotyped triggers. Adult women are more commonly affected, while childhood migraine has a greater prevalence in boys.

Most migraine is without aura, accounting for 80% of attacks. This means that no focal neurological complaints precede or accompany attacks; however, prodromal symptoms commonly precede migraines, and the physiologic basis for this is poorly understood. Prodromes are not included in the ICHD-2 criteria for migraine diagnosis. These prodromal symptoms

include yawning, food cravings (often for chocolate), mood changes including depression or euphoria, various gastrointestinal complaints involving diarrhea, cold hands and feet, and frequent urination. In Blau’s review on prodromes in 1980, he wrote that “George Eliot felt ‘dangerously well before an attack’ and Sir John Forbes had an ‘irresistible and horrid drowsiness’; Lady Conway ate her supper with a ‘greedy appetite,’ and DuBois Reymond’s migraines were ‘in general preceded by constipation’.” [2]

IHS Criteria for Migraine without Aura

- At least five attacks
- Headache attacks lasting 4–72 hours
- Headache with at least two of the following:
 - Unilateral location
 - Pulsating quality
 - Moderate to severe pain
 - Aggravation or avoidance of physical activity
- During headache at least one of the following:
 - Nausea and/or vomiting
 - Photophobia and phonophobia
- Not attributed to another disorder

IHS criteria notwithstanding, migraine headache is not always unilateral and not always pulsatile. Osmophobia, aside from photophobia and phonophobia, is common with migraine but is not a criterion for the diagnosis according to the ICHD-2 guidelines. Although not specific, the worsening of migraine with activity is the most sensitive criterion. The term *photophobia* describes the experience of an uncomfortable sensation of glare when exposed to light and often includes the effect of light enhancing the pain of

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Chapter 2: Migraine

migraine, both of which have a different physiologic basis. [3] These features explain the behavior of a sufferer during a severe attack: lying still in bed in a dark and cool room.

20% of migraineurs have an aura and the ICHD-2 criteria are as follows:

Migraine with Aura

- At least two attacks fulfilling criteria B-D
- Aura consists of one of the following no motor weakness
 - Fully reversible visual symptoms including positive and or negative features
 - Fully reversible sensory symptoms including positive and or negative features
 - Fully reversible dysphasic speech disturbance
- At least two of the following
 - Homonymous visual symptoms and or unilateral sensory symptoms
 - At least one aura symptom develops gradually over 5 minutes and or different symptoms occur in succession over >5 minutes
- Headache fulfills criteria for migraine without aura
- Not attributed to another disease

Intl Classification of Headache Disorders: 2nd edn. *Cephalalgia*. 2004; 24 (Suppl 1): 26–27. The international Classification of Headache Disorders. 2nd ed. *Cephalalgia*. 2004; 24 (suppl 1): 1–160.

Auras are predominantly visual, and if sensory systems or language become impaired, these phenomena usually follow visual aura. A migraine aura emanating from the occipital lobe is commonly experienced as scintillation, often followed rapidly by a scotoma. Fortifications are also common. The aura may begin in the center of a homonomous field, commonly enlarge and move across the visual field over 20 minutes, migrating to the periphery of one visual field, and then resolving. Recognizing their anatomic location in the cortex, these phenomena can be calculated to move at 2–6 mm/minute. After the aura there is a prolonged period of inhibition. This demonstrates a pattern of positive symptoms followed by negative symptoms, key in recognizing the episode as a migraine aura (Fig. 2.1).

The symptoms of migraine vary widely between attacks. Many practitioners and sufferers report only severe attacks as migraine. Some patients have frequent milder attacks as well, reflective of their lowered threshold for headache.

Attacks are often triggered by internal or external factors or a combination of both. Internal factors include menstruation, stress, and relaxation following stress, and sleep deprivation or oversleeping. External factors can include various foods including alcohol, missing a meal, smoke, change in weather, and certain visual patterns or scents. [4] Migraineurs are often bothered by the use of an optokinetic drum during a neurological examination. Vertigo and motion sickness are commonly associated with migraine, but motion can also be a trigger of an attack. Carsickness, particularly in children, is common. One study suggested that, in those having migraine with aura, light was a frequent trigger, and in women without aura, menstruation was a frequent trigger. [5] The Greek physician Paulus Aegineta in the sixth century AD wrote “each of these affections is a permanent pain of the head, liable to be increased by noises, cries, a brilliant light, drinking of wine or strong-smelling things which fill the head. Some feel as if the whole head were struck, and some as if one half, in which case the complaint is called hemicrania. When the affection is seated within the skull, the pain extends to the roots of the eyes, and when externally it spreads around the skull.” The trigger does not define the headache in that there are no actual *stress headaches*, *rainy day headaches* or *menstrual headaches*.

Migraine auras commonly precede the headache, but can develop in association with head pain. Some sufferers develop auras without any associated head pain. These episodes are often referred to as “acephalic migraines” and are more common after the age of 40. C. Miller Fisher described them as “late-life migraine accompaniments” but they can occur in younger individuals. [6] If these are periodically associated with head pain, a migrainous diagnosis can be made with increased confidence.

Sensory auras can occur as well as dysphasia or motor weakness. They may appear sequentially; the common order is visual auras first, then sensory auras second. Positive followed by negative features are characteristic. In the visual system, this is usually a scintillation followed by a scotoma. In sensory auras, this generally means tingling followed by numbness.

Pathophysiology

If migraine is a phenotype caused by multiple genotypes, the question arises: what is the final common pathway that defines a migraine?

It is often useful to view a migraine as a low threshold for the development of headache. Mundane triggers,