Migraine and Sleep: New Connections

By Andrew H. Ahn, M.D., Ph.D. and Peter J. Goadsby, M.D., Ph.D.

Editor's Note: *"Attack" is often a word associated with migraine, and for good reason. If you suffer from migraine headaches or know someone who does, you are well aware of its crippling nature. This story focuses on new research that has uncovered an important link between migraine and sleep patterns. A better understanding of the relationships among the body's circadian rhythms, the brain's hypothalamus, and a mutated gene holds enormous promise of improved care for the more than 36 million Americans who experience migraine (three times more common in women) and the number of people suffering from familial advanced sleep phase syndrome (FASP).*

The connection that scientists have made between migraine and circadian rhythm[1] is a brilliant example of how different fields with no apparent connection can receive a completely unscripted and unforeseen spark of insight, waiting only for the prepared mind to grasp the opportunity.

This tale starts in the earliest hours of the morning, before the first light of day. Many are the virtues attributed to the "morning lark." The songbird to which we refer is intimately associated with the earliest morning hours. For instance, Chaucer's "The Knight's Tale" speaks of "the bisy larke, mesager of day." Both American and British cultures extoll the moral virtues of the early riser. In 1670, in *A Collection of English Proverbs,* English naturalist John Ray noted, "The early bird gets the worm." Next came the 1735 edition of Benjamin Franklin's *Poor Richard's Almanack,* which also clearly identifies the material and economic rewards of early waking: "Early to bed and early to rise, makes a man healthy wealthy and wise." And so much the worse for us poor "night owls" who find our most productive hours after everyone else has gone to bed.

But before fully endorsing either the morning lark or the night owl, consider that biologists have found either trait may be less a matter of moral virtue and more a matter of brain physiology. Scientists interested in circadian rhythms have noted durable differences in activity pattern that distinguish the two metaphoric birds. The circadian rhythm is a biological clock that sets itself to daylight conditions and regulates many physiological signals, such as a morning surge of activity-promoting corticosteroids from the adrenal glands and a nighttime peak of sleep-promoting melatonin from the pineal gland. The clock implicates the hypothalamus, the phylogenetic, ancient part of the brain responsible for keeping the body working on an even keel. The hypothalamus's

homeostatic functions cover a range of critical physiological functions, such as body temperature, blood pressure, feeding and satiety, blood glucose, and the regulation of sex hormones.

Our Internal Clock

Circadian biologists have clearly established that even in the absence of daylight cues, the internal clock persists. Humans have evolved an internal circadian rhythm that corresponds closely to the 24-hour day cycle, but the range of normal circadian lengths includes both shorter and longer rhythms. Because people with shorter circadian rhythms arrive more quickly to the end of their day, they are said to have advanced sleep phase (ASP). Their internal rhythm both drives them to bed early and wakes them bright and early after a full night's sleep.

On the other hand, people with a long circadian rhythm, referred to as delayed sleep phase, are night owls. Their drive to sleep turns on later in the night, and they are likely to have trouble getting up in the morning because they have not had a full night's rest when most people are starting their day.

The circadian length not only varies from person to person but also tends to change over an individual's life span. It is somewhat longer during adolescence and early adulthood, and then it decreases with age.

Over the last decade, the recognition that the *extreme* morning-lark trait can run in families presented geneticists Louis Ptácek and Ying-Hui Fu with the opportunity to dissect the molecular pathways related to circadian rhythm in humans. This led to the revelation that a mutation of the

hPer2 gene—the human homologue of the period gene that regulates the daily rhythm of activity in fruit flies—is a key player in how the hypothalamus keeps track of the daily rhythm that drives our innate pattern of wakefulness and activity.[2] The significance of a common biochemical pathway underlying circadian rhythm throughout evolution cannot be overstated.

From a more individual perspective, it is also striking how the lives of people with a familial form of severe ASP (FASP) are deeply impacted by the burden of their hereditary condition. With a drastically short circadian cycle, their physiological "day" runs out early and drives them, and their family members, to sleep by 7:30 p.m. They report a lifelong pattern of activity that involves absolutely no night life, and arising after a very full night's rest at 4:30 a.m. It was further good fortune for scientists to find that two other family members with FASP had alterations of the gene CK1delta, an enzyme that is also implicated in the regulation of the *hPer2* gene in the hypothalamus.[3]

From Lark to Spark

Enter migraine, a complex brain disorder whose biology needs to be understood better. Migraine is a common type of disorder consisting of moderate to severe throbbing pain, and is often accompanied by other neurological symptoms such as nausea, vomiting, or sensitivity to light. Many migraine sufferers feel a throbbing pain only on one side of the head. Others experience an aura, a change in their sensory experiences, such as their vision, even before the headache begins. Migraine attacks last from hours to days and vary in intensity.

The spark of insight that brought the two fields together occurred recently when migraine researcher Robert Shapiro realized that his patient, who was seeing him for migraine with aura, was a member of an extended Vermont family of extreme morning larks.

A study of fourteen members of the family showed that the CK1delta gene implicated in FASP was also connected to migraine with aura.[4] Five family members who had identical mutations in the CK1delta gene also met the diagnostic criteria for migraine. The Ptacek and Fu team then sequenced this gene in the genetic material from 70 additional families with FASP. One family had a slightly different mutation in the CK1delta gene. In this family, too, all five members with CK1delta gene mutations had a history of headache that strongly suggested the diagnosis of migraine. To show that these changes in the CK1delta were in fact mutations, further biochemical studies were performed to show that the changes in both families reduced the enzymatic activity of the CK1delta protein.

While it was clear that CK1delta had a link to FASP through its regulation of the hPer2 protein, it took further arduous work to determine whether that relationship was merely coincidental or whether it indicated a causal role. Scientists used animal models to draw inferences of what can be known about migraine.[1] These models were at best approximations of a complex neurological disorder that includes pain and a host of sensory, motor, autonomic, gastrointestinal, and affective symptoms.

The details of this association, from a cellular or neurotransmitter point of view, still require further work, but neuroscientists are already buzzing about the news because the existence of a CK1delta-

FASP connection advances the likely role of the hypothalamus in migraine. In addition to the multitude of clinical associations between migraine and sleep, many other clinical features of migraine call attention to its connection to the hypothalamus.

In the lives of migraineurs—people affected by migraine—sleep is a key issue.[5] In fact, people with migraine commonly identify any disturbance from the normal routine of sleep as a trigger of migraine: staying up too late, getting up earlier than usual, changes in activity pattern due to shift work, jet lag, or even oversleeping. Accordingly, frequent or difficult-to-control migraine can be caused by any persistent disturbance of regular sleep, such as an erratic sleep schedule, frequent changes in activity due to shift work, frequent interruptions of sleep through the night, a chronic illness that disturbs sleep quality, or the presence of a sleep disorder such as obstructive sleep apnea.

As a result, two important components of effective management for people with frequent or severe migraine are identifying the trigger factors and aggressively neutralizing them. The major challenge is convincing the migraineur to make the often disruptive life adjustments that are needed to manage these triggers, and to give the changes enough time to assess their efficacy.

Migraine Triggers and the Smoking Gun

The many well-established trigger factors for migraine implicate the role of the hypothalamus in migraine, such as acute psychological stress, a skipped meal, overexertion with overheating, and lack of sleep. For most migraineurs, these are aggravating factors, not absolute triggers, meaning that a migraine does not follow them every time. These factors can be thought of as cumulative

physiological challenges that require the attention of the hypothalamus to normalize the physiological stresses that they represent.[6]

This background connects with further recent developments implicating the role of the hypothalamus in the regulation of pain. Among many examples, some of which may have implications for therapy, one recent line of evidence has shown that an antagonist to orexin, a peptide hormone associated with the regulation of feeding behaviors, can also suppress physiological responses to sensory stimulation to the head.[7]

Also, oxytocin (the so-called love hormone), a neuropeptide sometimes associated with social and nurturing behaviors in mammals, is thought to act on another hypothalamic regulator of blood pressure: the vasopressin receptor, which geneticist Jeffrey Mogil and colleagues linked to a genetic variant in the human population that can change responses to pain in men presented with a high-stress situation.[8, 9] Again, interestingly, early testing with a commonly available form of veterinary oxytocin can be administered by intranasal spray to abort a migraine attack. Two other neurotransmitters of the hypothalamus that have also caught the attention of those who study migraine include the sleep related hormone melatonin[10] and the pituitary adenylate cyclase-activating polypeptide (PACAP) [11].

Another independent line of brain imaging data also suggests that the hypothalamus may have an early causative role in the pathophysiology of migraine.[12] This study enlisted people with migraine who also have premonitory, or early warning symptoms prior to the onset of their attacks. They often note changes in mood or wakefulness, increased urination, yawning, or other changes that

again imply the role of the hypothalamus in the earliest phase of the migraine attack. In order to approach the premonitory phase experimentally, the migraine was triggered with a medication called nitroglycerin; considered by many researchers to be a useful tool for triggering a typical spontaneous migraine attack. Here again, the specific activation of blood flow in the hypothalamus during this early phase of the migraine attack, before the onset of headache, points a finger toward this important self-regulatory region of the brain for the initiation of the earliest aspects of the migraine attack.

The Road Ahead

The moral to this story can be summed up in what Louis Pasteur once said of observational scientific endeavors: "Chance favors the prepared mind." The link between migraine and sleep is, after all, a brilliant connection made by highly prepared and skilled investigators, working ever closer with many other collaborators. However, there are several other important points that stand in the backdrop. First, while there is still much work ahead of us to tease apart the mysteries of the hypothalamus and its connection to migraine, these converging lines of evidence provide some of the most original and exciting clues to date. Despite available therapies, further insights are urgently needed to inspire new therapies for the many who continue to suffer from this highly disabling disorder, one that needs to be prioritized more in line with its impact on society.

The impact, according to the American Migraine Foundation, is considerable. Medical care for the 36 million Americans who suffer from migraine accounts for up to an estimated $30 billion per year; American employers lose more than $13 billion each year as a result of 113 million lost work days due to migraine; nearly half of all migraine sufferers are never diagnosed and the majority do not

seek medical care for their pain. Migraine disproportionately affects women and those of lower socioeconomic status,[16] and chronic headache affects up to 36 percent of those returning from active combat duty in the conflicts in Iraq and Afghanistan.[17] Studies by the Global Burden of Disease, a project of the World Health Organization, found that migraine was a leading cause of life-years lost due to disability.[15]

Yet despite the huge social burden of migraine, very few resources are assigned to understanding and treating this condition.[13] One possible cause is that migraine is not considered a fatal condition. Another is that migraine is stigmatized, both in the media and by society, as an excuse to avoid work or commitments or "merely" a psychiatric condition.[14] Over the last decade, the National Institute of Health (NIH) has dedicated $1.8 billion to multiple sclerosis research. At present, NIH funding for migraine research is $15 million—less than 0.03 percent of the annual NIH research budget. Surely, funding needs to be more of a priority if we are to continue to build on these recent advances. But for now—from both a scientific and social standpoint—the spark of insight in making the connection between FASP and migraine is most welcome.

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