Chapter 7  
Miscellaneous

Case Studies in NDPH: New Daily Persistent Headache

Case History #1, Adult  Jack is a 42-year-old male, with no prior history of headaches or migraines, and is in good overall health. Two years ago, he awoke with a mild headache, which became severe as the day progressed. He had been experiencing cold type symptoms for about a week, had been under severe stress, and was not sleeping well. Jack now suffers from a moderate daily headache that is continuous, 24/7.

A workup by his general practitioner (GP) was completely normal. He visited a succession of doctors: his chiropractor, acupuncturist, physical therapist, dentist, and psychotherapist, all to no avail. He was prescribed various analgesics and headache preventives over the next 2 years, but found nothing that helped. After 2 years, a neurologist diagnosed Jack with new daily persistent headache (NDPH). Jack has lost his job due to the head pain, and his marriage is suffering. The next step is to try onabotulinumtoxinA (Botox) injections.

Case History #2, Adolescent  Rose is a 17-year-old female with no history of headaches. She presented with a severe headache that began suddenly 3 months prior, during finals of her junior year. A perfectionist, Rose is a straight A student who puts enormous pressure on herself. Rose has moderate anxiety, but no depression. She has a history of irritable bowel syndrome (IBS) that worsens under stress. Prior to visiting a headache specialist, she had not had a recent workup, nor had she seen an ophthalmologist. Her continuous headaches have interfered with school, and she is now homebound.

Her workup, consisting of laboratories, magnetic resonance imaging (MRI), and an ophthalmological exam, was normal. Topiramate was titrated to 150 mg, but it did not help, and produced intolerable side effects. Amitriptyline did help, but Rose gained weight and was very tired. Various abortives were utilized, but none was particularly helpful. A psychologist trained Rose in biofeedback, which was somewhat helpful for her head pain and IBS. Botox injections are being considered.
Introduction

New daily persistent headache (NDPH) is one type of chronic daily headache, along with chronic migraine, chronic tension headache, and hemicrania continua. NDPH is being increasingly recognized as an important type of headache, both because of the frequency and also the refractory nature of the head pain.

Onset and Symptoms

NDPH develops quickly, usually within hours or 1 day, but within 3 days the headache must be constant [39]. Many patients remember exactly what they were doing when the headaches began. The pain is usually bilateral, with aching pressure and/or throbbing. The intensity may vary from mild to severe, but tends to be mild to moderate. The headache is usually constant. At least half of patients describe migraine-associated features, such as nausea, phonophobia, lightheadedness, photophobia, etc. Allodynia, often seen in chronic migraine, is present in approximately a quarter of patients [37]. Autonomic symptoms (nasal stuffiness, conjunctival injection, etc.) may occur.

Diagnosis

NDPH is somewhat a diagnosis of exclusion. Infection (including meningitis and sinusitis), mass lesions, subdural hematomas, cerebral venous thrombosis, low or high cerebrospinal fluid (CSF) pressure headaches, arteritis, arterial dissection, posttraumatic, etc., all need to be excluded [10]. Usually the history, along with MRI/magnetic resonance angiogram (MRA), will exclude these entities. There are several newer proposed diagnostic classifications; generally, diagnosis includes:

- At least 3 months of sudden-onset headache
- No significant remission
- Exclusion of other disorders [14]

NDPH is unilateral in a small number of patients, and if this occurs with autonomic symptoms, it may represent a variant of hemicrania continua.

Pathophysiology

While we do not know the pathophysiology of NDPH, central nervous system (CNS) inflammation is one possibility. Tumor necrosis factor-α (TNF-α) has been implicated in neuro-inflammation. TNF-α is a cytokine that enhances inflammation. In one study, CSF evaluations of NDPH patients resulted in almost all samples showing an increase in CSF TNF-α [40].
Glial cell disruption may play a role; glial cells manufacture CNS cytokines. Glial cells are very sensitive to viral infection and stress; surgery may impact glials as well [11]. Cervical joint hypermobility, along with hypermobility of other joints, may play a role [42]. Patients with NDPH often are tall and thin, with long necks.

**Epidemiology**

CDH occurs in approximately 3.5% of the population, but the prevalence of NDPH is not known. One study from a headache center concluded that 10.8% of 638 CDH patients had NDPH [8]. A similar study in the pediatric population revealed that, among those with CDH, 13% had NDPH [19]. NDPH may well be more prevalent among adolescents than in adults. Females outnumber males with NDPH by approximately 2.5 to 1 [10]. Most patients do not have a previous history of headache. A prior history of anxiety or depression is seen in about half of the NDPH patients [10]. After the onset of NDPH, many patients experience depression.

**Triggering Events**

Approximately, 50% of patients have an identifiable trigger. Stress may be a trigger in some patients. Infection, particularly viral, is often cited as a trigger [39]. In one study, the Epstein–Barr virus was implicated as an initiating culprit [7]. Exposure to certain toxins may also precede the onset of NDPH. Surgical procedures have occasionally triggered the onset of NDPH. Head injury, even when mild, may be an initial event. Cervical trauma or other pathology, particularly in those who have thin necks with cervical hypermobility, may initiate the onset of NDPH.

**Treatment**

NDPH is more resistant to treatment than is chronic migraine, which is usually transformed migraine (slow onset over years). The usual daily preventive migraine medications are given, as they may be helpful for some NDPH patients. These include tricyclic antidepressants (amitriptyline, protriptyline, etc.), anticonvulsants (valproate, topiramate, etc.), antihypertensives (β-blockers, calcium channel blockers, etc.), Petadolex (natural butterbur), SSRIs (fluoxetine, sertraline, etc.), SNRIs ( duloxetine, venlafaxine, etc.), and muscle relaxants (tizanidine, etc.). OnabotulinumtoxinA (Botox) may be helpful as well; there are no published controlled trials of treatment for NDPH. Benzodiazepines, particularly clonazepam, have had some limited success. Intravenous dihydroergotamine (IV DHE) is more likely to be of help with chronic migraine. A course of high-dose IV corticosteroids, followed by oral steroids, has shown some promise, but the high doses can predispose to serious side effects [36]. IV magnesium may provide short-term relief. Doxycycline, given over several months, may help some patients with NDPH. Greater occipital nerve
blocks sometimes are useful, particularly with unilateral headaches. Sphenopalatine-ganglion (SPG) frontal blocks, with the newer devices SphenoCath, Allevio, or Tx360, may help.

Outside of medication, psychotherapy is worthwhile for those with anxiety or depression. Biofeedback is helpful for some headache patients. Exercise is always encouraged, as is yoga and Pilates. Acupuncture, physical therapy, or chiropractic may help for some patients.

While the results of treatment may be discouraging, it is crucial to stick with the patient, continue to try different medications or modalities, and not to give up on the NDPH sufferer.

**Long-Term Prognosis**

Several studies have evaluated long-term outcomes. One study revealed that, after 2 years with NDPH, about 25% of the patients were free of headache, and 66% had at least a 50% reduction in pain levels [33]. Another study reported that 76% of patients continued to have headaches over time, while 15% remitted; median time to remission was 21 months. Eight percent had a cyclic form, with a relapsing-remitting pattern. A small study of children and adolescents discovered that 8 out of 28 patients were free of headache within 1–2 years, while most (20) continued to suffer long-term from head pain [53].

**Conclusion**

NDPH is an important category of headache, as it is often difficult to treat, and results in considerable disability. It is unique in that more than 50% of patients have an identifiable trigger, although these range from infection to surgery to head trauma. We are just beginning to identify the pathophysiology that leads to NDPH. Treatment of NDPH is scattershot and varied at present; further studies will undoubtedly lead to more effective therapies. Note this is a version of an article that originally was published in *Practical Pain Management*, Vol. 12, July 2012.

**The Immune System and Headache**

*This chapter finds that the immune system plays a key role in migraine pathogenesis and that manipulation of immune system elements may be a promising area of development for new headache therapies.*

The involvement of the immune system in chronic headache has been speculated upon since the 1970s [47, 48]. Various components of the immune system have been examined in relation to headache [13, 25]. While great strides have been
made in advancing our understanding of neuroimmunology, the complexities of the system make its specific role in headache pathology unclear. This chapter describes some of the key elements in the immune system and their relation to headache pathogenesis.

**Calcitonin Gene-Related Peptide**

Calcitonin gene-related peptide (CGRP) is an inflammatory neuropeptide involved at every level of migraine pathophysiology, including the meninges, trigeminal ganglion, trigeminocervical complex, brain stem nuclei, thalamus, and the cortex. Upon initiation of migraine at the brain stem or cortex level, neurogenic inflammation occurs such that peripheral trigeminocervical neurons are activated. We then observe a release of CGRP and other neuroinflammatory peptides. CGRP induces neurogenic vasodilation that leads to further plasma protein extravasation (PPE) and the influx of mast cells and other pro-inflammatory cells [21]. The process of neurogenic inflammation sensitizes the peripheral nociceptors transmitting via the trigeminal axon, through the brain stem and the thalamus, and finally into the cortex.

In animal models, CGRP is released following stimulation of the CNS—similar to what is observed in migraine. Triptans inhibit the animal’s CGRP release. In humans, injections of CGRP into migraine patients result in delayed headache. Certain studies have suggested that relief of migraine corresponds to a reduction of CGRP levels in the blood and that migraine-specific therapy with triptans decreases CGRP [45]. These studies have led to the development of CGRP-receptor antagonists that could conceivably block neurogenic vasodilation in the meninges. CGRP activity in the trigeminal ganglion may limit vasoconstriction.

Two CGRP-receptor antagonists, olcegepant and telcagepant, were tested for the abortive treatment of migraine; unfortunately, their development is on hold [22]. There are ongoing studies of monoclonal antibody injections, once per month, for the prevention of migraine.

It is possible that onabotulinumtoxin type A (Botox) may work via anti-inflammatory neuroimmune mechanisms. The effect of Botox may partially be due to its effect on CGRP, or other similar inflammatory compounds.

**Cytokines**

Recent studies have revealed that the neuropeptide CGRP triggers the secretion of cytokines via stimulation of CGRP receptors found on T cells [5, 23]. Cytokines are involved in inflammation, in modulation of the pain threshold, and also in trigeminal nerve fiber sensitization. In small trials, cytokines have been proven to precipitate headache [51].
In trials where TNF was injected, headaches were shown to be induced while, on the other hand, the TNF antibody was shown to reduce pain in humans [54]. Plasma levels of both pro- and anti-inflammatory cytokines are enhanced during migraine attacks. TNF levels increase after migraine pain onset and decrease progressively over time after the onset of the attack [34]. Plasma levels of a pro-inflammatory cytokine, interleukin (IL)-1, are also enhanced after the initiation of headache. IL-1 release is induced by TNF and may lead to hyperalgesia. The amount of an anti-inflammatory cytokine, IL-10, has also been shown to increase after the onset of a headache and may be involved in analgesia. One study revealed IL-10 inhibited release of TNF, which is antinociceptive [49].

Cytokine levels in the CSF of migraineurs have been studied with varied results. Increases in IL-1 receptor antagonist (IL-1ra), monocyte chemoattractant protein-1 (MCP-1) and transforming growth factor-1 (TGF-1) were measured in patients with migraine and episodic tension-type headache (TTH) versus pain-free controls. Rather than being the cause of headache, changes in the level of cytokines in the CSF are thought to be due to pain [4]. No correlation has linked increased cytokine levels to a decrease in pain and there has not been a difference found in cytokine levels with migraine versus episodic TTH [4].

**Tumor Necrosis Factor**

TNF is a pro-inflammatory cytokine involved in inflammation and it is crucial in the activation of pain. A small number of patients with NDPH develop symptoms after viral infection. It is possible that a pro-inflammatory cytokine such as TNF could initiate and maintain CNS inflammation even after the infection resolves. Rozen et al. [41] reported elevated levels of CSF TNF in 19 of 20 NDPH patients, in 16 of 16 chronic migraine patients, and in 2 of 2 chronic tension headache patients. The study suggests that TNF plays a role in the etiology of these types of headache. Refractory chronic daily headache could involve increased levels of CSF TNF. Patients with NDPH (and, theoretically, elevated TNF) often are refractory to a variety of medication regimens.

TNF is important in a number of conditions such as sinusitis and rhinitis, as well as headache [6]. The development of drugs that modulate TNF may prove beneficial to these conditions as well as headache.

**Adiponectin**

Obesity is a known to be a major risk factor for the development of chronic migraine [35]. Adipose tissue secretes adipocytokine adiponectin, which is believed to modulate several inflammatory mediators important in migraine. A large amount of adipose tissue leads to decreased secretion of adiponectin [16]. Adiponectin has a protective role in limiting the development of insulin resistance, dyslipidemia, and
atherosclerosis. It also has an anti-inflammatory action through inhibition of cytokines IL-6 and TNF-induced IL-8 production. Adiponectin induces the production of cytokine IL-10, which is anti-inflammatory. Adiponectin decreases migraine but, paradoxically, a sudden increase may worsen a headache [35].

**Glia and Headache**

Recent studies have shown that glial cells, previously thought to serve only a supportive role, are now known to directly influence the microenvironment of trigeminal ganglion neurons through gap junctions and paracrine signaling [46]. Following trigeminal activation, CGRP secreted from neuronal cell bodies activates adjacent glial cells to release nitric oxide (NO) and inflammatory cytokines which, in turn, initiate inflammatory events in the trigeminal ganglia that lead to peripheral sensitization [6, 26]. The neuronal glial signaling is thought to be an important process, ultimately leading to the initiation of migraine. The glial modulation of neurons through immune mediators is an unexplored area for new migraine medications. An excellent report on glia research by Drs. Moskovitz and Cooper appeared in these pages in the November/December 2010 issue [31].

**Mast Cells**

It is generally accepted that migraines are partially mediated by prolonged activation of meningeal nociceptors (pain receptors). One possible explanation of how this occurs seems to be found in the physiology of mast cells. Mast cells are granulated immune cells that play a critical role in inflammation. They have been found to reside in high density in the intercranial dura, a peripheral tissue covering the brain [8]. Mast cells are located in close proximity to the blood vessels and the primary afferent nociceptive neurons.

When the mast cells are stimulated, they degranulate their contents into the local milieu. This activates the surrounding trigeminal meningeal nociceptors and promotes a prolonged state of excitation. It is not clear if there is a specific molecule released from the mast cells that is responsible for the propagation of migraine. Several of the degranulated molecules have implications for migraine. The list includes histamine, leukotrienes, the cytokines TNF and IL-6, and endothelin-1 [43, 15].

Once the meningeal nociceptors are activated by the release of mast cell molecules, they propagate a cascade of neuronal activation by releasing neuropeptides (e.g., CGRP, substance P). These activate and further degranulate residual mast cells and thus prolong the migraine headache. According to Levy et al. [24], the key lies in the increased expression of the phosphorylated form of the extracellular signal-related kinase (pERK). This is an anatomical marker for nociceptor activation and downstream signaling of the spinal trigeminal nucleus.
Seasonal Allergies and Headache

The association between seasonal allergies and headaches has been well documented in several studies [9, 1, 30, 52, 32, 29]. A recent study found that headaches are 1.5 times more common in those with atopic conditions (asthma, seasonal allergic rhinosinusitis, chronic bronchitis) than those without these disorders [1]. This relationship suggests that inflammatory changes in the nasal and sinus mucosa of individuals with seasonal allergic rhinosinusitis could be a potential trigger for migraines. Allergies may also partly explain the seasonal variation experienced by many migraine sufferers. However, several primary headache disorders, including migraine, are at least partly characterized by the presence of cranial autonomic symptoms (e.g., conjunctival injection, lacrimation, eyelid edema, rhinorrhea, nasal congestion, postnasal drip, and reddening of the face and ears) which closely resemble the signs and symptoms of seasonal allergic rhinosinusitis [9]. This overlap in symptomatic presentation can make it quite difficult to clinically distinguish headache secondary to seasonal allergic rhinosinusitis from primary headache associated with cranial autonomic symptoms. Accurate characterization of these headaches through a detailed history and physical examination is crucial since appropriate treatment highly depends upon a proper diagnosis.

Many patients who believe they have sinus headaches are suffering from migraine. In fact, sinus headache is the most common misdiagnosis of patients with migraine [9, 28, 3, 35]. For its part, the International Headache Society (IHS) does not recognize sinus headache as a diagnostic entity—unless it is associated with a confirmed diagnosis of underlying acute rhinosinusitis.

Conclusion

The immune system plays a key role in migraine pathogenesis. The involvement of CGRP is important in neurogenic vasodilation, peripheral sensitization, and the initiation of the migraine cascade. Various cytokines, including TNF, IL-1, and adiponectin, have been implicated in the precipitation of migraine.

The role of allergies in migraine remains a confusing area. In headache-prone individuals, seasonal allergies may be a trigger and most people diagnosed with sinus headaches are actually suffering from migraine.

The earliest work on the immune system and headache focused on mast cells and their role in propagating the cascade of neuronal activation when degranulated. The supporting glia cells, long thought to be inert, have been found to modulate neuronal activity—partly through immune mediators. The manipulation of immune system elements is a promising area of development for new headache therapies, although these may be many years in development. Note this originally appeared in Practical Pain Management, Vol. 11, Jan 2011.
Weight Loss

Weight loss and exercise may help headaches. Develop a long-term approach.

Different approaches work for different people. Permanent weight loss is difficult. It takes changes in lifestyle and behavior. It never comes about through wishfully thinking, “I need to lose a few pounds and exercise.” It comes about via a concerted effort in which exercise and weight control become an important project in your life. You need to get up every morning committed to your program, focusing on how to get your needed exercise and sticking to your diet.

Key steps to maintaining a weight loss are:

• Grazing (eating small meals throughout the day while reducing portions at meal-time).
• Portion control (measure or weigh your food) *Portion control is crucial!* You cannot exercise off bad nutrition!
• Count calories or points. (Weight Watchers is a good program, as is the www.sparkpeople.com website.)
• Weigh yourself often.
• Eat foods that are low in fat, sugar and salt, and high in fiber.
• Do *not* diet. Severely restricting food is related to the yo-yo syndrome, where weight is frequently lost but quickly regained. When you fall off the wagon, get right back on your diet/exercise program; it is crucial to *not* let bad days turn into weeks and months. Diets do not work.
• Motivation is a key; dietitians/nutritionists can help. Fitness/health magazines are motivating. One good newsletter is the Nutrition Action Newsletter (www.cspinet.org). Apps such as myfitnesspal are helpful.
• The old Weight Watchers motto to “Move more and eat less” is still relevant. The Weight Watchers app is excellent.
• Exercise regularly; it has to be “fun”; people who view it as “exercise” eat more afterward
• The “turtle” wins the weight loss race.
• Try a “Fitbit” step counter (or other similar type).

Weight loss supplements (over the counter) do not work. For a review of these, and natural products, www.consumerlab.com is an excellent site. Medicines that may help weight loss:

1. Topiramate (one of the main migraine preventives): decreases appetite.
2. Stimulants: phentermine (and others) help; these are best used short term.
Exercise: Just do Something and Have Fun!!

Exercising may decrease headaches. It is certainly crucial for weight loss. To get most of the benefits of exercise, you only need to think of exercising in small chunks of time, even 10 or 15 min. Most people are able to fit exercise more easily into their lives when thinking this way. We are looking for a total of 20 min daily on average. The more the merrier. Some people do well counting total minutes of exercise from Monday to Sunday, including everything (walking, etc.). Used fitness equipment places have good, inexpensive bikes.

It helps to have a routine, whether it is regular walks, classes, or equipment to use at home. A stationary bike is easy to use; you can read or watch TV while riding, and even 5 or 10 min at a time will add up. Studies have shown that short intervals of exercise throughout the day can be as effective as doing one prolonged session. I think that the old mantra of “getting your heart rate up to a target #, for an intense hour” actually kept people from exercising; the idea is to just do something, anything, for any period of time.

If you do not enjoy what you are doing, you will not continue it. Health clubs are great, and the classes are motivating. Pilates is core work, and is crucial for preventing back pain, and falls, as we age. There are DVD and Cable TV Pilates, but live classes are best. Five or ten minutes of Pilates or core work, three or four times per week, helps quite a bit. Yoga is also very good, and can help with stress and headaches. Even 5 or 10 min of yoga posing are beneficial. Consider using a personal trainer.

Remaining active throughout the day is also important. People who are moving throughout the day instead of sitting are in better shape than those who sit all day and exercise only at night. Standing at the computer may help the core, and taking frequent breaks from sitting is important. The Fitbit (or similar step counters) are motivating and helpful.

Many people get into diet and exercise, for a period of time, and then out of it. Getting back into exercise takes some inertia, such as just walking (or a stationary bike) for 5 min. Just do something for a few days, and you will get back “into it.” Do not worry about “going to the club and getting my heart rate up and exercising hard for an hour.” Just dive back in with baby steps.

Supplements for Good Health (in Headache Patients)

Vitamin D is important to take; everything else is very iffy

Most herbal and vitamin supplements have not held up to scrutiny in controlled trials, and some have turned out to be harmful. A number of well-done studies have linked multivitamins and antioxidants (the supplements) to an increase in cancer, among other problems. Do not believe the advertising claims: Multivitamins and many other supplements are not necessary for good health, and could be harmful. www.consumerlab.com/ is an excellent site for info on vitamins and herbs. Even omega-3 capsules are now implicated in causing cancer. Antioxidants, particularly
A, C, and E, have been linked to high rates of cancer. Vitamin B and C can actually give you headaches. The only vitamin truly holding up to scrutiny is Vitamin D.

Vitamin D is important for our skin and bones, and may help fight hypertension and autoimmune diseases. Recently, adequate levels of vitamin D have been linked to lowered rates of cancer, especially colorectal cancer. People who live in cold climates are often low in vitamin D, as they are not in the sun enough. Most need to take a vitamin D supplement. The latest studies suggest that adults need at least 2000 international units a day. Avoid the generic vitamin D; use a name brand. The Nature Made brand available everywhere is US Pharmacopeia (USP)-certified and is an excellent brand. If you take calcium with added D, you probably still need to take an extra D supplement. Do not take more than 4000 units of vitamin D without consulting your physician.

Omega-3s (Fatty Acids) Many studies have shown the benefits of omega-3s (natural, not capsules) for the heart, for moods, and possibly for headaches. Eating fish twice a week is a good goal, particularly fatty fish such as salmon, tuna, trout, and mackerel. Other sources of omega-3s in the diet are tofu, soybeans, walnuts, and canola oil. It is better to get omega-3s naturally than from supplements. In fact, the supplements have been linked to increased cancer rates. We do not recommend the omega-3 supplements!

Calcium is necessary for the heart, muscles, and nerves to function and for blood to clot. Low intake of calcium leads to the development of osteoporosis and is associated with high rates of bone fractures. Absorption of calcium decreases as we age. Eating too much salt and protein, especially animal protein, increases calcium loss. It is much better to get calcium in foods than in supplements. Calcium supplements have had side effects, and should be taken only if you cannot get enough calcium in foods.

Calcium is found in milk, yogurt, cheese, broccoli, tofu, beans, sardines, calcium-enriched fruit juices, fortified cereals, etc. Our systems cannot absorb more than 500 mg of calcium at a time. Calcium in the form of calcium citrate, such as citracal, is more easily absorbed than calcium carbonate. Citracal caplets plus D are a good form of calcium (315 mg) plus vitamin D (200 IU). The usual dose is one or two tablets, once or twice a day; consult your physician. To learn more about calcium, visit www.health.nih.gov.

Aspirin If you are at risk for heart disease, your doctor may recommend a daily dose of aspirin. Its properties may help prevent heart attacks, strokes, and even headaches and certain cancers. The usual dose is one aspirin (325 mg) a day.

Generic aspirin is fine. Taking a baby aspirin (81 mg) or a half-tablet of regular aspirin (162 mg) may be sufficient; the dose varies by person. Aspirin can cause stomach ulcers; if it hurts your stomach or causes heartburn, stop taking it and consult your doctor.

Coenzyme Q10 (CoQ10), for people on statins, is a crucial compound, important for your heart, muscles, and nerves. It is naturally produced by your body. However, the statins (cholesterol-lowering drugs like Simvastatin, Lipitor, Pravachol, Vytorin, and Crestor) deplete the body’s CoQ10.

Studies have indicated a possible benefit from CoQ10 for migraine and the heart. We suggest taking 200 mg per day of CoQ10 if you take one of the statin drugs. It
has not yet been proven that this helps the muscles, but CoQ10 is generally safe and may prevent headaches.

**Resources** An excellent newsletter, Nutrition Action Health Letter, is inexpensive (Visit www.cspinet.org). A good website for healthy living is www.sparkpeople.com, with more than a million members. We also like www.consumerlab.com.

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**Chaos (Nonlinear Dynamics) and Migraine**

*Note: This article is included primarily for interest sake, and also because chaotic mechanisms may be important in migraine pathogenesis. In the future, medications that influence chaotic dynamics (such as glial cell modulators) may allow for a greater effect with less drug.*

By affecting chaotic (nonlinear) controls—whereby a tiny change in initial conditions may lead to a profound difference later in the process—new therapies may be employed that use less drug in the migraine cascade than is currently required.

The brain works primarily via synapses that interpret incoming inhibitory and excitatory impulses and nonlinear dynamics are involved in the feedback system of these complex neuronal systems. Physiologically, for energy conservation, it would make sense for living systems to utilize a nonlinear system, rather than random or simple linear dynamics. By utilizing a system where a tiny change in initial conditions may result in a major difference “downstream,” a great deal of energy may be conserved. Chaos is a subset of nonlinear systems. Low-dimensional chaos theory may be the only way to explain how complex neurological systems are adaptable, efficient, versatile, and have effective feedback homeostasis. A large body of evidence has indicated that electrical activity of the brain, heart rhythms, blood glucose levels, and glycolysis are all governed, to some extent, by chaotic dynamics. Characteristics of chaotic systems include:

1. Extreme sensitivity to initial conditions; a tiny change upstream may lead to an enormous difference downstream. This would have major implications for headache therapies, as influencing the neuron’s initial conditions would require much less drug than attempting to affect all of the components later in the cascade.
2. The deterministic, not random, nature of chaotic dynamics. Chaotic output of a deterministic system, when plotted, mimics randomness but is not random and, in that sense, “chaos” is a misnomer.
3. Chaotic systems possess a small number of independent variables, and the output is complex and deterministic.
4. The behavior of a system partially controlled by chaotic dynamics may change dramatically with a tiny change in the value of one parameter and is called a bifurcation.
5. The sequence of data in a chaotic system may be plotted and viewed as a phase space set.

To demonstrate chaotic mechanisms takes an enormous amount of data but this chapter will simply describe the possible role of chaotic dynamics in headache pathophysiology [27, 20].
Background

Chaos is a math-based, nonlinear dynamical theory. Chaos has been used to predict the behavior of ion flow, as well as neural and biosystems. Chaos is a misnomer, as it is deterministic, not random. A key property is extreme sensitivity to initial conditions so that a tiny change in initial conditions results in huge changes downstream. This has advantages for biosystems, particularly in conserving energy. Chaos has been shown to govern the beating of the heart, as well as the evolution of epileptic seizures.

Ionic flow is governed by either random, linear, or chaotic (nonlinear) controls. Chaotic control means that a small change in the channel protein results in a large change in the channel protein shape. This saves energy as compared to a simple linear control system. Ionic dynamics are crucial in cortical spreading depression (CSD). A tiny change in K\(^+\) efflux, or Ca\(^+\) influx, will result in a large effect downstream, with CSD and oligemia. Chaos has been demonstrated to play a role in K\(^+\), Ca\(^+\), and Na\(^+\) movements. Tiny perturbations—possibly brought about via weather, stress, or hormonal changes—in the hyperexcitable brain may result in CSD and eventually in PPE. Only chaotic dynamics could logically explain the cascade that leads from CSD to PPE.

The drugs that affect CSD may influence the membrane through chaotic controls. Drugs that better control chaos may inhibit CSD. For instance, by affecting K\(^+\) efflux through small effects upstream, we may prevent the events downstream that lead to headache. This has been demonstrated to be true with epileptic seizures. Peripherally, the familiar cascade of Mg\(^+\) binding to N-methyl-d-aspartate (NMDA), with subsequent Ca\(^+\) influx, is very sensitive to initial conditions and changes. Drugs that work through chaotic controls peripherally may be effective in very small concentrations.

With central sensitization (CS), windup is a typical system that is probably controlled by a nonlinear flexible system (chaos). Linear dynamics could not explain or control windup. Different aspects of CS are most likely under chaotic control, from NMDA activation to nitric oxide synthesis. Thalamic recruitment involved in expansion of the pain area is best explained by chaos. The pathological shift of homeostasis seen in chronic CS, with a loss of brain stem inhibition, may actually reflect a loss of chaotic control. This is similar to the loss of control in the heart, resulting in v-tachycardia. The brain stem periaqueductal gray (PAG)—important in migraine—has been shown to be under chaotic control through P/Q-type Ca\(^+\) channels. Chaos may assert its most profound effects in the brain stem.

Chaos and the Nervous System

Chaotic dynamics has been proven to function at a variety of levels in the nervous system. Both individual neurons (particularly in squid giant axons), as well as in neuronal systems, have been shown to be—at least some of the time—governed by nonlinear dynamics. Neuronal networks of thalamocortical circuits have their feedback loops managed by chaotic dynamics. Neural network models in analyzing
thalamic networks have demonstrated the presence of chaos. In a person with epilepsy, when chaos fails and patterns become too regular, an epileptic seizure may result to return brain dynamics to a more normal (chaotic) state. By the very nature of generators of complex neural behaviors, they cannot be random but must be deterministic and nonlinear, at least some of the time. It is likely that neuronal dynamics vacillate and totter between random, linear, and chaotic dynamics [27].

Chaos theory may help us understand why a patient experiences a severe headache associated with a weather change or other headache triggers.

**Chaos at the Ionic Level**

The flow of ions about the cell has been determined to be a combination of randomness, linear (deterministic) movements, and chaotic processes. Again, for energy saving, chaotic mechanisms are more efficient. Chaotic mechanisms in the brain stem may explain why tiny changes in weather or hormones may result in a migraine. Most neuronal activity in the brain stem involves postsynaptic inhibition that has been demonstrated to be governed by chaotic mechanisms. If we were dealing with a linear system, a tiny change in weather, stress, hormones, or sleep would not lead to neuronal activity differences. Chaotic dynamics will turn tiny initial changes or perturbations into major events, possibly triggering CSD. By altering the concentration of sodium outside of the cell, it has been demonstrated that the membrane response must be governed, at least in part, by chaos. Several studies have demonstrated chaos at the cellular level in the brain [44]. By utilizing the “jumps” of ions through the energy barriers of the channel protein, maps have been constructed that reveal the chaotic controls. Numerical solutions and algorithms have been constructed revealing when the transition to chaotic dynamics occurs [27].

Ion channel kinetics, partially controlled by chaotic dynamics, play a crucial role in CSD and in brain stem inhibition. A small change in the channel protein will result, through chaos, in a major difference in the shape of the protein. Neurons in the cortex fire with irregular patterns. Part of what governs the spiking patterns is the balance between excitatory and inhibitory inputs. The spiking patterns have been proven to be governed by chaotic dynamics, at least some of the time.

**Chaos at the Neuronal Level**

Single neurons, as well as groups, fire in a variety of patterns, from regular oscillating patterns to bursts (and everything in between). Neurons, and neuronal systems, undergo transitions that carry them between diverse states [50]. Chaotic dynamics partially govern both individual neurons, as well as groups of neurons. The chaotic dynamics switch the neurons from one firing pattern to another. In the presence of low concentrations of serotonin, neuronal firing patterns change, with an increase in “beating” periods, all of which is consistent with chaotic dynamics. The synchro-
nized dynamics of groups of neurons take the form, at times, of low-dimensional chaos. The presence of chaos has been proven to be a factor in the inhibitory synaptic noise of certain types of neurons. Experimental studies have shown that chaos is involved in the dynamics of central dopaminergic neuronal systems, particularly in the substantia nigra [40].

**CSD and Chaos**

CSD induces calcium and sodium influx, with potassium efflux and P/Q calcium channels involved. It is much too delicate and complex to be run by a random mechanism or simple linear kinetics. Chaotic controls have been demonstrated to be involved with these channel ionic movements. Chaos would also aid in explaining some of the properties of CSD. The initiation of CSD may be brought about by a very tiny change in potassium—with activation of receptors and resulting in a large change downstream thus causing CSD and oligemia. With the potassium efflux under (partial) chaotic control, the chaos probably helps to regulate the increased cortical hyperactivity inherent in the brain of some migraineurs. There is evidence that the PAG may be partially controlled by chaotic dynamics.

A tiny cortical input may result in activation of the trigeminal nucleus caudalis, with resultant release of pro-inflammatory peptides and a release of glutamate. CSD leads to PPE, with a very small perturbation upstream leading to this cascade. Only chaotic dynamics may explain how this sequence may be possible. The drugs that affect CSD (topiramate, amitriptyline, sodium valproate) may influence chaotic dynamics through membrane effects. It requires significantly less drug to influence the system if chaos is involved versus a system that is primarily governed by linear (or random) dynamics. As is the situation with epileptic seizures, preventing the propagation of impulses upstream, through tiny ionic changes, may lead to less of the headache cascade downstream.

**Sensitization**

The pathological shift of homeostasis that is observed with chronic CS and a loss of brain stem inhibitory activity may actually reflect a loss of chaotic control. This is similar to a loss of chaotic controls in the heart leading to certain arrhythmias, or with a loss of chaos leading to a seizure.

Glutamate is the most prevalent excitatory neurotransmitter in the brain and, along with calcium, is crucial in positive feedback processes. Glutamate has been shown to be directly involved in bidirectional communications between neurons and astrocytes. Research has demonstrated that glutamate feedback processes are critical in the generation of complex bursting oscillations in astrocytes. These glutamate-mediated events are likely to be involved in memory storage, epilepsy, and migraine. The control of this feedback process may well be, at least partially,
enacted through chaotic control. Peripherally, the familiar cascade of magnesium binding to NMDA, with subsequent calcium influx, is very sensitive to minute initial changes [17]. Chaotic controls would help to explain the dynamics of peripheral sensitization. Drugs that may influence chaotic dynamics could work peripherally in very low concentrations.

Simple nonlinear dynamics could not possibly explain the phenomenon of wind-up. NMDA receptor activation, as well as thalamic recruitment, would best be explained if they were controlled by nonlinear membrane/ionic dynamics.

**Controlling Chaotic Dynamics**

By utilizing and influencing chaotic dynamics, significantly less drug would have to be employed, versus the amount required to affect a linear system. Brain-derived neurotrophic factor (BDNF) is a neurotropin that modulates the excitability of neuronal membranes. One study utilized BDNF to affect hippocampal neurons. It has been demonstrated that the patterns of electrical activity in hippocampal neurons are governed, in part, by chaotic dynamics. The hippocampal electrical system is a deterministic, chaotic one, with a few degrees of freedom. This “neuronal chaos” may be sensitive to change by the application of small amounts of materials, such as BDNF, that influence temporal spiking. In this study, the application of BDNF to cultured hippocampal neurons enhanced the reliability of spike timing and resulted in more stereotyped firing patterns. It was felt that BDNF influenced chaos through effects on sodium at the membrane level. BDNF enhanced membrane conductance and thus stabilized the membrane. The application of BDNF affected the switching between periodic and aperiodic neuronal oscillations. BDNF has been linked to modulation of neuroplasticity. The BDNF application decreased irregularity of firing patterns by modulating neuronal outputs as well as inputs. The result was a BDNF-induced chaos stabilization. This experiment with BDNF was the first one to demonstrate a pharmacological stabilization of chaos at the neuronal level [12].

**Practical Applications**

In several areas of medicine, practical applications for chaos-type mathematical models are beginning to emerge. One company, Vicor Technologies, Inc., is utilizing a device (the PD2i) to identify patients at high risk for sudden cardiac death. This unit employs chaos theory to determine risk. In addition, the company is developing a similar device, using chaotic dynamics, to evaluate the health of the autonomic nervous system in patients with diabetic neuropathy.

Chaos theory may help us understand why a patient experiences a severe headache associated with a weather change or other headache triggers. Tiny perturbations in a migraineur’s delicate autonomic nervous system may lead, after the familiar cascade of migrainous physiological events, to a migraine.
A number of studies have been done to identify the role, if any, of patent foramen ovale (PFO) in migraine. There may be an association, albeit not yet clinically proven, between PFO and migraine. Two current headache trials in Europe and North America (“Premium” and “Prima”) are blinded, sham-controlled PFO closure studies. If indeed an association is proven, chaos theory may help to explain the relationship between PFO and migraine. A tiny (downstream) change in blood flow may lead (upstream) to a migraine attack.

To apply chaotic dynamics to pain or headache, we will need a great deal of basic research. The potential exists to create drugs that may utilize chaotic dynamics. For instance, glial cells modulate much of what goes on in the CNS. Glial cells utilize a small amount of neurotransmitter to modulate a large number of neurons. Future medications that affect glial cells may be effective through chaotic dynamics.

**Conclusion**

The physical dynamics involved at the neuronal level, both intra- and extra-cellular, are too complex to be explained via random, or even linear, dynamics. Chaotic dynamics certainly play a role, at least some of the time. It has been demonstrated that chaotic dynamics help to govern individual neurons as well as neural systems. One fundamental principal of chaotic dynamics, unlike simple linear systems, is that a tiny change in initial conditions may lead to a profound difference later in the process. Only chaotic dynamics may explain why a tiny change in weather, stress, hormones, or sleep may result in a migraine. Chaos has been demonstrated to be involved in heart rhythms. Chaotic dynamics may also explain why a PFO may result, upstream, in an increase in CSD and headache. It is possible that, by utilizing and affecting chaotic controls, new therapies may be employed that utilize less drug than is currently required. Note this is a version of an article that was originally published in *Practical Pain Management*, Vol. 10, May 2010.

**Suggested Reading**