MIGRAINE 101

WHAT IS MIGRAINE?

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Although migraine actively afflicts approximately 38 million Americans-well over 10% of the general population-and every day is the subject of countless conversations, publications, web sites, advertisements and jokes, surprisingly few people (including medical providers) can offer an accurate answer to the simple question: What is migraine?

The term "migraine" is easy enough to define. If you've had 5 or more attacks of unprovoked headache (not the headache of a tequila hangover) that lasted 4 to 72 hours, was severe enough to inhibit or even prohibit your routine daily activities, was accompanied by nausea or light/sound sensitivity and could not be attributed to another medical disorder…you are a migraineur.

The headache of migraine is not always severe, throbbing or one-sided

Note that this definition does not require the headache to be throbbing or lateralized to one side of the head. Although such clinical features are common in migraine, they are far from invariable. Plenty of migraineurs have headache pain that is "all over the head", constant/non-throbbing or both.

Nor does the diagnosis of migraine require the occurrence of aura symptoms (eg, visual "stars", "flashes", "zig-zags" or blind spots). Only 20-25% of migraineurs ever experience aura, and in that subgroup there are relatively few who experience aura with each and every migraine attack.

Finally, the headache of migraine is not always severe, and some migraine attacks may involve no headache whatsoever (eg, migrainous aura without headache). With many episodes of migraine the headache may be mild in intensity, lack any associated nausea or light/sound sensitivity and symptomatically resemble tension-type headache more than what we usually think of as migraine.

This tendency to characterize only severe headaches as "migraine" can complicate the medical provider's attempt to accurately determine a migraine patient's total headache burden, the key to developing an appropriate treatment strategy. When questioned regarding their headache frequency, migraine patients often base their estimate only on those headaches that are severe and incapacitating. In doing so they may fail to include headaches that are non-disabling but nonetheless decrease work productivity and quality of life. Reluctant to overstate the impact migraine is having on their lives, patients discount those days when they manage to "carry on" despite a headache…but can neither work at full-speed nor take any real pleasure in a social event they otherwise would enjoy.

Again, when migraine patients underestimate their headache burden, this works against the provider's effort to provide them with an effective management plan. However severe the headaches involved, a migraine patient who is experiencing only 3 "headache days" per month requires a very different treatment approach than the patient who not only averages 3 days of incapacitating headache each month but also is experiencing daily or near daily head pain of mild to moderate intensity.

WHAT CAUSES MIGRAINE?

For many years it was believed that migraine attacks arose from changes in the blood vessels which supply the head and brain. Aura (when it occurred) was attributed to constriction of arteries, with the neurologic symptoms of aura reflecting decreased blood flow to retinal or brain tissue. The throbbing, sickening pain of migraine in turn was attributed to a compensatory dilation of those and other vessels.

We now believe that migraine is genetic in origin and that the disorder represents a genetically-induced hypersensitivity involving neurons (brain cells) located within the central nervous system. If a genetically primed neuron is triggered by a change in the external environment (eg, a sudden drop in barometric pressure) or internal environment (eg, a sudden drop in estrogen level), that neuron may depolarize (discharge electrically) and, by triggering its neighboring neurons to join in, induce the pathways in the brain that normally conduct head pain to awaken and produce the familiar symptoms of a migraine attack.

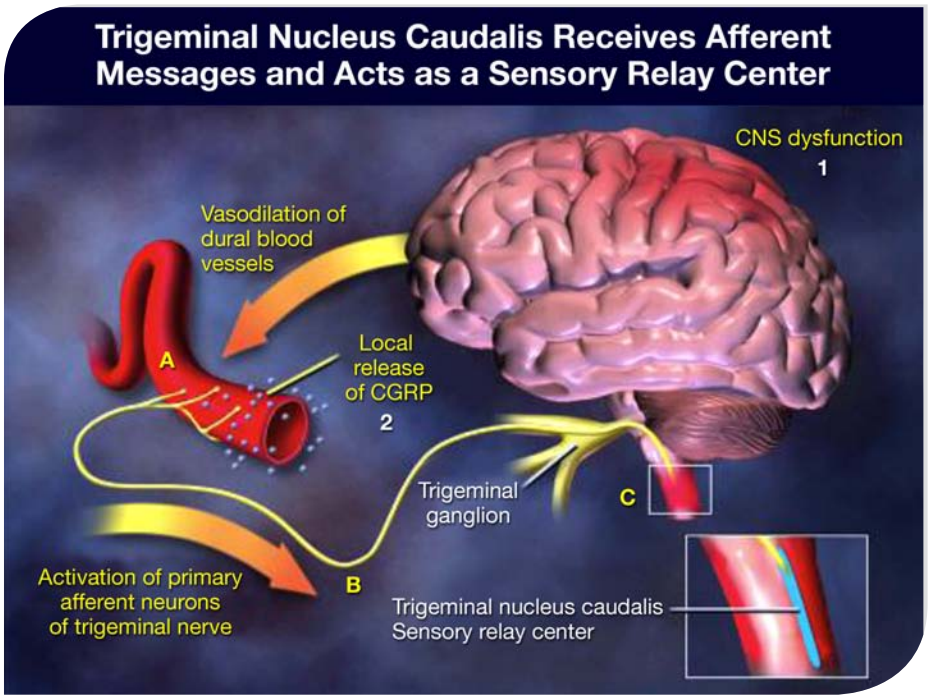
The biologic circuitry of migraine is illustrated below. Under normal conditions, a painful stimulus produced by, say, trauma or meningitis, activates head pain receptors located on blood vessels (A) within a membrane (the dura) that lines the brain. Those receptors generate a pain signal that is transmitted by the trigeminal nerve (B) to the trigeminal nucleus caudalis (C), a cluster of neurons located within the brain stem. The trigeminal nucleus caudalis (TNC), acting as a relay station, passes the pain signal upward to the brain itself, and at that point there is conscious awareness of headache.

MIGRAINE'S BIOLOGIC WIRING DIAGRAM

In migraine, the normal flow of head pain signaling is reversed. In response to a change in the internal or external environment, genetically hypersensitive neurons located in the visual cortex of the brain (1) fire off electrically, generating a pain signal that travels brain-to-dura, against the normal flow of head pain conduction: downward to the TNC in the brain stem and out the trigeminal nerve to the blood vessels within the dura. When the signal reaches the junction between the nerve and blood vessel, it stimulates the release of proteins (2) such as CGRP (calcitonin gene related peptide) that in turn cause the vessel to dilate and to leak other proteins that promote inflammation. That inflammatory response further stimulates the already sensitized trigeminal nerve endings, producing another pain signal that bounces back (B) to the brain in the normal direction of sensory flow (dura>brain).

Thus a migraine attack can be thought of as a physiologic "ping pong match", with pain signal flowing simultaneously in opposite directions, "inside>out" (brain>dura) and "outside>in" (dura>brain). Each signal reinforces the other, with the signal amplifying as the transmission pathway becomes increasingly sensitized. The individual suffering the acute migraine attack correspondingly experiences a progressively more severe headache. This biologic and clinical process will persist until the underlying pain signaling system spontaneously becomes inactive or the afflicted individual takes action to terminate the attack (eg, goes to sleep or takes a medication such as a triptan).

If this system of migrainous head pain transmission becomes chronically sensitized, the migraineur will begin to experience more frequent episodes of head pain. In the worse case scenario, episodic migraine may "transform" into chronic migraine, and the migraineur may suffer a constant headache of relatively low intensity with superimposed attacks of more severe head pain. In such cases a course of preventive (prophylactic) therapy may be required to stabilize the transmission system (see *How can migraine be treated?* later in this article).



In their physiologic origins and their treatment, migraine and epilepsy are biologic 1st cousins. Both conditions involve brains that contain abnormally sensitive neurons, and in both the source of this sensitivity may be genetic. Migraine and epilepsy are "bi-directionally co-morbid" (ie, if one has migraine, he or she is more likely to have epilepsy than normally would be expected...and vice versa). Further cementing this relationship is the fact that several of our best medications for migraine prevention were first developed to treat epilepsy (egs, divalproex sodium/Depakote and topiramate/Topamax, Trokendi).

In short, while changes in the caliber and permeability of cranial blood vessels may play an important secondary role in generating migrainous symptoms, **migraine is a primary brain disorder**.

HOW TO TREAT MIGRAINE

Given what we now know about its cause, effective treatment of migraine must necessarily involve stabilization of this genetically primed brain and nervous system pathway for head pain transmission that has become acutely or chronically sensitized.

When we speak of acute (or symptomatic) migraine treatment, we are referring to measures one may take at the time of a headache that are intended to terminate that headache and associated symptoms such as nausea and light sensitivity. Preventive (or prophylactic) treatment refers to measures used on a chronic basis to reduce headache burden.

Reducing chronic stres, good sleep hygiene and avoidance of obvious migraine triggers may do as much as any prescription therapy to reduce migraine attack frequency

There are many ways to skin the migraine cat, both for acute/symptomatic treatment and for chronic/prophylactic therapy. While non-prescription (OTC="over the counter") and prescription medications are often of great value in controlling migraine, there are other ways to treat the disorder that do not involve administering a pill, nasal spray or injection. Regular aerobic exercise, other measures taken to reduce chronic stress (egs, yoga, meditation), good sleep hygiene and avoidance of obvious migraine triggers may do as much as any prescription therapy to reduce migraine attack frequency and overall headache burden. Especially when utilized early, aerobic exercise, application of heat or cold to the head and neck areas, drinking a caffeinated beverage or just briefly taking a break and relaxing may terminate an acute attack.

ACUTE MIGRAINE TREATMENT

If medication is used to treat acute migraine headache, several important caveats should be considered.

- **Match medication(s) to headache intensity**

For example, oral triptans generally work best for headaches of mild to moderate intensity, but injectable sumatriptan is more effective for "rescue" from a severe migrainous headache. You probably need to keep multiple pharmacologic "weapons" on hand to treat the varying intensities of migraine headache you experience.

- **Treat early**

2-3 aspirin taken with a caffeinated beverage early in an attack may be more effective than a narcotic taken when the headache has become well-established and severe.

- **Administer an adequate dose**

For example, OTC ibuprofen is available in a 200 milligram (mg) strength and naproxen sodium in a 220 mg strength. Both drugs can be quite effective for early treatment of acute migraine headache, but "migraine doses" are generally 600-800 mg for ibuprofen and at least 440 mg for naproxen sodium; with either, co-administer caffeine (see below)

- **Consider the route of drug administration**

Acute migraine attacks are accompanied by gastroparesis, meaning that the stomach's usual motility is reduced to the point that it may not pass orally administered medications that "drop in" on to the small intestine where they would otherwise be absorbed, enter the blood stream and speed their way to their intended targets to relieve your acute migraine head pain. Erratic gastrointestinal (GI) absorption of oral medications for the treatment of acute migraine may at least partially account for the therapeutic inconsistency many individuals experience with their use.

To some extent the problem with gastroparesis/impaired GI absorption may be circumvented by administering the oral medication with a caffeinated beverage or by taking a compound medication that contains caffeine (eg, Excedrin). Some prescription medications for acute migraine (eg, Treximet) are formulated so as to speed up their exit from the stomach and subsequent absorption into the bloodstream.

If your migraine headache is accompanied by nausea and vomiting, then an orally administered medication obviously is a loser. At such times you can resort to acute migraine medication that is administered intranasally or by subcutaneous injection.

- **Avoid chronic overuse of any given medication (or class of medications) for acute migraine**

Virtually all of the medications used to treat acute migraine headache, OTC or prescription, may actually promote headache if used too often on a chronic basis. Patients often refer to this clinical phenomenon as "rebound" headache, but it is more accurately characterized as *medication overuse headache* (MOH). Ironically, the first class of medications synthesized specifically for acute migraine treatment, the triptans (eg, Imitrex=sumatriptan), are especially prone to causing MOH if chronically overused. Others, such as "narcotics" (opiates and opioids) and butalbital-containing compounds (egs, Fiorinal, Fioricet, Esgic) not only cause MOH may but also block the therapeutic effect of migraine prevention therapies. As a rule of thumb, to avoid making a bad problem worse, use no one acute migraine medication or class of medications more than 9 days per month on a chronic basis.

PREVENTIVE (PROPHYLACTIC) MIGRAINE THERAPY

There are also important caveats to keep in mind if preventive therapy is prescribed to chronically stabilize the biologic migraine pathway and thus reduce headache burden.

- **Take your preventive medication as prescribed**

Skipping doses of an orally administered medication for migraine prevention or

taking a lower (or higher) dose than prescribed may work against you, preventing any positive treatment response, encouraging side effects and even serving to increase your headache burden. If you are receiving Botox injections for suppression of chronic migraine, the intervals between treatments typically should not exceed 12 weeks; extending those intervals beyond 12 weeks may give the migraine pathways a chance to "recover" and become re-sensitized, and before you know it you'll be back to your miserable pre-Botox baseline.

- **There's no guarantee of success.**

No one preventive therapy is effective for all migraineurs, and your friend's or relative's remarkably positive response to a given therapy does not ensure you will have the same experience. In addition, all allopathic therapies for migraine prevention have potential side effects, and one patient may enjoy a wonderful therapeutic response to a particular treatment whereas the next will suffer a bag-full of annoying side effects and absolutely no reduction in headache burden. Unfortunately, medical providers currently lack much in the way of a means to predict which patient will respond well versus poorly to a particular therapy, and both acute and preventive migraine treatment thus remains a process of educated "trial and error".

- **Continue treatment for an adequate duration**

Don't expect immediate success. Some oral medications for migraine prevention require a gradual upward escalation of their doses to reach what is required for an optimal therapeutic response, a process that may take weeks to accomplish. Even if such escalation is unnecessary and you get take a therapeutic dose from the get-go, it may take a month or more to determine whether the medication is going to be effective for you.

Unfortunately, it's during those first few weeks of treatment with an oral prevention therapy that side effects from the drug tend to be most prominent. It's discouraging to be experiencing side effects but no benefit, but stick with the treatment if possible. Talk it over with your provider. Sometimes a temporary reduction in dose will help you through the rough patch.

If you are receiving Botox injections for migraine prevention, remember that many patients with chronic migraine do not begin to experience any reduction in headache burden until after the second set of injections. Don't give up after only one treatment.

- **Treat break-through headaches aggressively**

Seldom is a migraine prevention therapy so effective that it will completely prevent all headaches from occurring. If you have an acute headache despite prevention therapy, treat that headache! Use the same strategy outlined earlier under Acute migraine treatment.

- **Don't stick with a loser**

If you've given the prevention therapy a real chance; if you've taken an adequate dose for an adequate duration or, in the case of Botox, if you've received at least two treatments separated in time by no more than 12 weeks; and if you still are stuck with a substantial headache burden that is eroding your quality of life... *do something*! Perhaps you need a higher dose. Perhaps a different dosing regimen (say, twice daily rather than at bedtime only). Perhaps a different therapy altogether. Whatever. If you're not making progress, it's time for a change.

SUMMARY

This, then, is the essence of migraine: its clinical definition, its underlying biologic cause and its treatment. Study this migraine primer, take away from your reading the major points made, and you will know more about your disorder than 90% of health care providers. More important, you will be prepared to take an active role in effectively managing your migraine.

CGRP: WHY ALL THE FUSS?

Calcitonin Gene-Related Peptide (CGRP), a protein which is the most potent naturally occurring dilator of blood vessels in the human body, plays a vital role in the circuitry which produces migraine headache.

Point-to-point communication within our nervous systems relies on electrochemical transmission: a electrical signal passes down a conducting "wire" (ie, a nerve), and when that signal reaches its target at the nerve ending, a chemical neurotransmitter is released to connect with a receptor located on the nerve's target. In the case of migraine, the "wire" is the trigeminal nerve, the chemical neurotransmitter is CGRP and the target is a head pain receptor located on a dural blood vessel.

The CGRP antagonists are experimental large molecule monoclonal antibodies or small molecules that either block CGRP directly or block its receptor. Now under investigation for their safety and effectiveness in treating acute migraine and preventing headache in episodic or chronic migraine, they are highly selective agents that prevent closure of the migraine circuit at a key point in the pathway that generates head pain.

Five different pharmaceutical companies (Alder, Allergan, Amgen, Lilly and Teva) are racing to bring their CGRP antagonists to market for general clinical use. According to the antagonist involved, administration may be oral, subcutaneous or intravenous. The results from research conducted to date have been highly promising, and the CGRP antagonists may well represent the next great breakthrough in migraine therapeutics.