Literature Review in Typical Migraine

Hunter White
hewhite@iastate.edu

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Abstract:

What is known of the pathogenesis and pathophysiology of the onset of only typical migraine is discussed. This includes familial hemiplegia headaches and migraine with or without aura. This does not include common tension headaches or other common headaches not involved in similar pathogenesis to the trigeminovascular pathological pathways causing migraine. The format is a general discussion on current theories on migraine pathophysiology, current pharmaceutical therapies and statistics on typical migraine.

Introduction:

“A masters student in Biomedical Sciences visits his professors during office hours, not yet eager to go over course material (although certainly soon) but to make them aware that he suffers from acute episodes of migraine which often become debilitating and force him to miss class. He lays out the details of this condition to his instructors in hopes that they are willing to work with him should interference with coursework arise. The student, in order to earn his master’s degree, decides to investigate the problem that affects him and millions of other migraineurs in order to help other migraineurs and non-migraineurs alike improve their understanding of this often overlooked, highly prevalent class VII disability.”

Migraine is an episodic headache disorder affecting 38 million people in the U.S.; 8.6% of males and 17.5% of females (Doulberis, Michael et al) and 324 million worldwide according to the World Health Organization report on the Global Burden of Disease. Migraine sufferers, often referred to as “migraineurs”, report varying degrees of pain, recurrence, symptoms and associated causes of their migraine attacks (Davidoff). Each migraineur’s experience with migraine is different and the degree to which it inhibits daily functioning varies significantly. In the same report, the WHO rates severe migraine, along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disorders. (Michael) It is also one of the top three overlooked prevalent conditions in the world, right along with anaemia and hearing loss. Health care for patients with migraine cost nearly $11 billion per year to directly treatment and nearly $12 billion in indirect costs for missed work hours and other expenses (Loder). Due to this detriment to our society, this review aims to describe what migraine is, current treatment options and future options according to research.

Even though migraine is one of the oldest disorders known to man, its pathophysiology and pathogenesis has never been fully understood. The condition was prevalent in ancient Egyptian society, dated in records as early as 1200 B.C. (Mandal). Hippocrates referred to the ocular disturbances of scintillating scotoma in some of his works, describing the moments of relief from migraine attacks after intense pain and episodes of emesis. Credit for the discovery of migraine is given to Aretaeus of Cappadocia, who described in the second century further clinical symptoms such as unilateral pain in the cranium (Mandal). Modern research on the topic has led to better experiments and drug development for migraine sufferers. However, discussed later in this review, there is only one drug on the market currently approved by the FDA targeting specific neuropeptides related to migraine development.
General Pathophysiology

No proposed mechanism fully encompasses what occurs during a migraine. However, the majority of findings agree on these assumptions:

1. Predisposition for migraine exists in familial lines, suggesting the condition is a multi-genic polymorphism and complex interactions occur at the level of gene expression.
2. The mechanism which causes migraine is not the same between every migraineur as only about one-third of sufferers experience aura; the frequency of attacks, magnitude of pain and response to treatment varies between individuals.
3. Most research accepts the four phase structure to explain pathophysiology but it should be mentioned that there is often overlapping and variability (Charles).
4. The vascular theory, neurogenic theory and neuroinflammatory theory all likely contribute to describing the complexity of migraine pathophysiology. Other propositions such as the sino-rhinogenic pathway also warrant further study.

Vascular Theory

Three primary theories on the pathological mechanism of migraine exist and it is considered that all three play some role in the mechanism of migraine attacks. The oldest is the vascular theory, first observed by Harold G. Wolff in the 1950s, observing that cerebral vasoconstriction of blood vessels with cortical spreading depression leads to a depolarization event of neurons across grey matter of cortical regions of the brain which can cause an ocular deficiency referred to as aura. Aura is seizure-like symptoms of temporary hallucinations seen as blind-spots in combination with visualization of scintillating, jagged lights and lines that fill portions of the visual space. Aura is followed by a compensatory mechanism of vasodilation of these blood vessels, leading to a throbbing pain experienced shortly after the migraine onset. Today, most theories agree in the premonitory phase, vasoactive peptides are released from primary sensory nerve terminals innervating meningeal blood vessels. They activate perivascular trigeminal nerves and cause dilatation of arteries in meninges as well as perivascular inflammation and extravasation of plasma proteins. First-order neurons terminate in the trigeminal nucleus caudalis in the brain stem. They activate second-order neurons that ascend to the thalamus and from there, third-order neurons project to higher cortical centers. If uninterrupted, this process causes pain and can lead to hyperalgesia and allodynia, both hallmarks of prolonged migraine attacks (Goadsby).

Neurologist Harold G. Wolff led pioneering experiments to come up with a comprehensive set of assumptions about migraine symptoms in 1963 (Davidoff). Wolff concluded from his studies that symptoms were strongly associated with vascular problems. His three assumptions: 1. visual auras transiently regressed when cerebra vasodilation was induced by amyl nitrate administration or by inhalation of 10% CO2 and 90% O2 (Marcussen RM).
During the headache, the amplitude of the superficial temporal artery pulse increased, and concomitantly, the throbbing or pounding quality of the pain migraine correlated with these increases in pulse amplitude (Davidoff). 3. Ergotamine, which reduced the pulsations of the superficial temporal artery, relieved the migraine pain (Graham). Although novel findings, these assumptions do not come without scrutiny. The problem with Wolff’s studies was that he had no way of studying cerebral blood flow directly so everything was based indirectly on clinical evidence. They also fail to address the pathogenesis of triggering (chemical) events of vascular dysfunction. Therefore, this theory cannot act alone in describing migraine pathophysiology. This is where the neurovascular theory is introduced.

**Neurovascular Theory**

The neurovascular theory is based on the observation of an event described during MRI scans called cortical spreading depression, often abbreviated SD. During SD, neural inhibition due to a cascade of potential chemical mediators and a pro-inflammatory response cause sporadic and pulsating spread of neuronal depolarization across cortical regions. SD traverses the cerebral cortex grey matter at a velocity of 2-5 mm/min. This process could either directly or indirectly activate the aura phase and trigeminal afferent projections to brain areas associated with nociceptive processing (Parsons), which in turn cause headache. During this event, effects on perivascular nerve activity from SD results in the release of substances such as calcitonin gene related peptide, neurokinin A, substance P, and NO. These substances produce blood vessel dilation, protein extravasation and sterile inflammation, stimulating the trigeminocervical complex. The vascular theory describes that high levels of extracellular potassium is present in the cortical regions of the brain, leading to reduced blood flow and possible trigger of the compensatory action of vasodilation phase. This is thought to be the final event leading to the onset of pain in the cerebrum.

**Neuroinflammation Theory**

The neuroinflammation theory focuses specifically on the chemical mediators that act on vaso- and nociceptive receptors in the brain. The neuroinflammation theory describes the role of neuropeptide release in cerebral regions that ultimately cause pain as described in previous theories, such as neurokinin, SP and CGRPs. These peptidyl signaling molecules have major effects on the function of the trigeminal nerve, which is one of twelve cranial nerves that influences feeling and homeostasis mechanisms for the cranial region in humans. This theory is one of the least understood by researchers because clinical observations in humans are hard to test. Mouse and culture studies are the best approaches to researching this topic until the role of individual signaling molecules is better understood. In addition, most drugs developed for prevention and treatment are based on the activation or deactivation of neuronal cells affected by these molecules.

Substance P and calcitonin gene related peptide are two neuromodulators with receptors throughout the central nervous system that play some role in the cascading events of migraine. Substance P is a modulator of pain and nociception. It antagonistically binds to neurokinin-1 receptors. In mouse studies, it shows signs of vasoconstrictor properties along with antidepressant and anxiolytic properties. However, evidence is lacking on the impairment of substance P-mediated neurotransmission in depression and CSF studies in depressed patients are not agreed upon. Calcitonin gene-related peptide, CGRP, is a longer vasoactive and nociceptive regulatory peptide located in both central and peripheral neurons (Edvinsson). It has been well
established that CGRP is a potent vasodilator and it is thought that its physiological role is to help control blood pressure. It may also be involved in olfactory, auditory, vision, and pain pathway, and contribute to learning, feeding and other behaviors (Keiffer). CGRP inhibits T-cell proliferation by inhibiting IL-2 production while stimulating the production of cytokines such as IL-6, IL-10 and TNF. In macrophage, it inhibits antigen presentation and other macrophage functions inducing phagocytosis (Van Der Kleij). CGRP antagonistic antibodies are being produced to test efficacy in reducing migraine attacks for some individuals. The drug Erenumab is the only FDA approved CGRP-receptor antagonist on the market in the US.

Aspects of all three theories work to describe the mechanism involved in migraine. With all three theories in mind, the goal in migraine research is to alter an event in the cascading pathophysiology to eradicate symptoms of migraine. There are a select number of drugs which aim to do this, while most drugs taken for the treatment of migraine have to do with blocking nociceptive pathways occurring only in the migraine phase.

**Sinus Hypoxic Nitric Oxide Theory**

A fourth theory on the sino-rhinogenic pathway as a possible pathogenesis for migraine has shown warrant for study in the near future. Besides substance P and CGRP, nitric oxide is a class IV neurotransmitter produced from glycerol trinitrate to work as a vasodilator. Starting from the known trigeminal nociceptive impulse in the migraine, two main peripheral trigeminal nerve activating mechanisms may induce migraine. First the nerve endings of the nasal mucosa which are directly stimulated by diffuse paranasal sinus nitric oxide are indirectly stimulated by vasoactive substances released by antidromic activation of the nerve, parasympathetic efferent of the nerve and sterile neurogenic inflammation. Secondly, the perivascular nerve of nasal mucosal and the meningeal blood vessels are directly stimulated by either diffuse paranasal sinus nitric oxide or by shear stress mediation. Moreover, sino-rhinogenic impulses may mediate to disruption of inhibitory sensitization modulated of sensory input and cause sensory hyperexcitability. In addition neuronal stimulation proposed by some migraine hypotheses could also give rise to migraine headache when the sino-rhinogenic vulnerable factors induce the migraine pathophysiology. (Bandara). Bandara suggests that migraineurs should have a comprehensive sino-rhinological examination performed as a standard surgical and medical management of migraine that links with the sinus hypoxic nitric oxide theory may restore the hypoxic state or reduce or remove the paranasal sinus nitric oxide diffusing surface.

**Symptoms**

Ocular disturbances such as aura, described also as scintillating scotoma, hypersensitivity to light, sound and smell (Noseda); nausea, and a number of autonomic, cognitive, emotional and motor disturbances (Olesen) are noted as main disturbances reported by migraineurs. Noseda and Burstein characterize much of the throbbing pain associated with migraine to be a result of dysfunction of the trigeminovascular pathway, suggesting there is a strong connection between neurogenic and vascular pathways that lead to the throbbing pain. Other lesser known symptoms that are linked to premonitory phase (Griffin et. al.) changes include: episodic depression, anxiety, craving for food, insomnia and hyper- or hypoactivity. Many migraineurs report these phenomena preceding the actual aura or pain that comes with a migraine attack. Mild numbness
and tingling of extremities, allodynia, nausea, emesis and other underlying symptoms like hyperactivity vary in characterization between migraineurs but are often attributed to stimulation of dopaminergic and serotonergic pathways. These pathways are either an inciting cause or are stimulated downstream by trigeminovascular changes. Little is known on the exact mechanism behind this but the efficacy of triptans and antidepressants as migraine prophylactics identifies another connection in this complex disorder.

**Triggers of Attack**

Of what little is truly understood on the underlying mechanism of the pathophysiology is the same in the case of pathogenesis. Many migraineurs believe they have identified foods in their diet containing particular compounds as tyrosine (a vasodilator), mood disorders such as depression and mania linked to serotonergic imbalances, and bright lights or sounds are often identified as triggers in patients. No studies have shown significant correlations between these pathways but it is early to make a definitive statement. It is possible that these assumed triggers can be explained by the behavior observed in the premonitory phase when the onset of an attack is inevitably forthcoming. However, documented internal and external triggers in those at a genetic predisposition for migraine include, broadly: stress, hormonal fluctuations, sleep disturbances, meal skipping or sensory overload (Kelman, Levy). All of these factors are believed to have the ability to alter the excitability capable of activating cascading pathophysiological pathways of the trigeminovascular system (Coppola, Pietrobon, Stankewitz). Some link their triggering events to stress due to overexhaustion, sleep deprivation and other factors.

The same often occurs with food. Many migraneurs believe they are allergic to certain ingredients in food that trigger their migraine so they avoid certain foods they believe to contain those ingredients, such example as chocolate or alcoholic beverages. Chocolate is the most frequent food cited by patients as a trigger and is listed by many authors as a major precipitant of migraine attacks (Dalton, Hanington, et al.). A hypothesis is that the potent vasoactive amine beta-phenylethylamine, also found in some fermented foods, is the chemical responsible for inducing headache attacks (Schweitzer). Chocolate also contains a complex mixture of other compounds such as phenolic compounds, which includes: tyramine, octopamine and serotonin (Schweitzer). However, these studies are far outdated and one possible conclusion is that cravings for chocolate or other food/beverage is likely an unrecognized prodrome as the attack had already started, patients are not aware because they have not reached the aura or headache phase (Davidoff). The common conclusion on dietary triggers in migraine is that compounds identified as vasodilators or vasoconstrictors may play a role in pathogenesis but not enough data is available to make a definitive statement.

**Aura**

Aura, also recognized as scintillating scotoma, is the first sign of a migraine attack as a prodrome for about one-third of migraineurs (Shams, Plant). When an aura occurs, the first sign is typically a small “blind-spot” that occurs at or near the focal point of the visual field. This spot is described as less than that of a spot, rather a lack of perception of anything at that particular point in the visual field. Within the next five to ten minutes, the spot begins to expand and take the shape of a curvature with scintillating zig-zag lines and shapes. This shape morphs, expands and sometimes multiplies in the visual field for 5-45 minutes and then settles as blurriness of the
peripheries before the visual field returns to normal. Residual blind spots may persist in the field of vision and hypersensitivity to light may exacerbate these effects. The widely accepted theory is that cortical spreading depression (SD), is a wave of neuronal hyperactivity followed by cortical depression which accounts for the aura (Lauritzen, Ataya). A study by Hadjikhani and colleagues reveals that migraine aura is in fact neuronal, likely evoked by aberrant firing of neurons and related cellular elements characteristic of SD and is not evoked by ischemic conditions (Hadjikhani).

It is believed that this dysfunction has associations with the ophthalmic division (CNV-1) of the trigeminal nerve (CNV) as the trigeminal nerve plays other key roles in the mediation of migraine at other stages of the cascading effects. Typical migraine headache with aura has not been reported following enucleation or evisceration of the eye which suggests the visual disturbances experienced originate at the visual cortex (Gupta). The conclusion of one study suggests that migrainous scintillating scotoma and headache result from mechanical deformation of corneo-scleral envelope. No drug has been developed to stop an aura once begins but preventative migraine therapy drugs that target to lessen the occurrence of migraines can also lower the occurrence of migraine associated auras.

Genetic

The role of genetics in identifying individuals with disease or at a predisposition for a disorder such as migraine must be taken into consideration. Although characteristics for migraine seem to be familial, genome-wide association studies have not yet identified any genetic alterations with large effect sizes (Nyholt). A total of 38 genomic loci have been associated with migraine in population studies (Gormey). Migraine is caused by a complex interaction between genetic and environmental risk factors. The disorder phenotype co-segregates with mutations in genes commonly cited which include: CACNA1A, ATP1A2, SCN1A, KCNK18 and NOTCH3 (Rainero). The analysis of genotype-phenotype correlation in migraineurs has several confounding factors and thus far, only polymorphisms of the MTHFR gene have shown an effect on migraine phenotype (Rainero). More studies need to be conducted to clarify the complex interactions of polymorphisms with phenotypic expression.

Drugs - Treatment

Triptans

Triptans are serotonin 5-hydroxytryptamine (5-HT1B/1D) receptor antagonists that have had the most effective prophylactic response in the treatment of moderate to severe migraine. Triptans are not effective in the aura phase of migraine and are most effective when taken within 1-2 hours of the onset of the headache phase and before allodynia for the most effective treatment. Triptans were originally thought to cause cranial vasoconstriction to stop headache pain by action at postsynaptic 5-HT1B receptors on the smooth muscle cells of blood vessels (Loder). The new hypothesis is that triptans bind to presynaptic 5-HT1D receptors on nerve terminals and on dorsal horn, blocking release of neurotransmitters that activate second-order neurons that otherwise reach the thalamus (Levy). The idea is that they facilitate descending pain inhibition systems in the central nervous system. It is estimated that triptans are effective in 60% of non-responders to NSAIDS (Linde) and there is no significant difference in efficacy between the seven types of triptans. Triptan drugs are approved for both oral and subcutaneous
administration. Patients have the option of subcutaneous injection, which is especially useful when unable to keep down a pill due to vomiting.

Other specific methods for pharmaceutical treatment of migraine include ergotamine (an ergot alkaloid) and nasal dihydroergotamine (DHE), which both show analgesic effects. Often times, ergotamine drugs will be paired with caffeine as a powerful cranial vasoconstrictor. This treatment option is typically reserved for patients when the individual shows little or no response to triptans as the primary treatment option (Silberstein). Oral administration is typical but epidurals are available when nausea and vomiting are a risk. The nasal DHE is typically reserved as a third option to treat moderate or severe migraine when other options do not show efficacy. This medication can be administered intranasally or through IV injection. These treatment options are not uncommon because the onset of a migraine is best treated early using a high dose on the therapeutic ladder to try to combat nociceptive pain receptors early in the pathogenesis.

Non-specific migraine medications include simple analgesic approaches and subsequent combination analgesic therapies if pain persists. Analgesics such as aspirin, ibuprofen or paracetamol are usually first choice for patients who perceive a mild migraine attack. Reviews show that 1000mg paracetamol in combination with 10mg metoclopramide has the same short term efficacy as 100mg sumatriptan on mild attacks (Derry). This same data shows that aspirin is well tolerated at up to 1000mg and non-steroidal anti-inflammatory drugs such as naproxen, diclofenac, etc. have been shown to have similar efficacy with mild attacks. Combinations of acetaminophen, aspirin and caffeine under drug names like Excedrin are often the first choice in treating acute migraine. It is safe to take simple and combinational analgesics within label dosage guidelines along with sumatriptan due to their differences in mode of action.

Preventative Treatments

Drugs that show efficacy in preventing migraine nociception and/or frequency of attacks are often prescribed to migraineurs who deem it necessary to combat migraines to maintain daily functioning. Patients who try preventative therapies should know that these drugs may not stop all attacks or prevent the aura phase. However, two-thirds of patients can expect a 50% reduction in headache frequency (Moja) and that treatment drugs may be necessary when an attack does occur. These factors should be hep doctor and patient determine if preventative therapy is beneficial:

1. Migraine attacks become debilitating >2 per month, having a significant impact on lifestyle.
2. Treatment drugs are not fully effective and are at risk of overuse.
3. Patient shows desire to try pharmacological steps in preventing migraine attacks.

Beta-Adrenergic Blockers

Beta blockers are a widely used class of preventative treatment for migraine and their interaction with the events of migraine are not understood. A study of beta blockers and riboflavin by Peter Sandor and colleagues aimed to investigate the influence of pharmacological treatments on the intensity dependence of auditory evoked potentials in migraine. The rationale is that patients with migraine show abnormal cortical information processing and decreased brain mitochondrial energy reserve. Both of these are relevant for study of migraine pathogenesis and could be modified with drug therapy. Results from treatment with beta blockers showed the
intensity dependence of the auditory evoked cortical potentials was significantly decreased (before: $1.66 \pm 1.02 \mu V/10 \text{ dB}$; after: $0.79 \pm 1.06 \mu V/10 \text{ dB}$, $P=0.02$). The decrease in intensity dependence was correlated significantly with clinical improvement ($r=0.69$, $P=0.02$). There was no change in intensity dependence after riboflavin treatment (before: $1.80 \pm 0.81 \mu V/10 \text{ dB}$; after: $1.56 \pm 0.83 \mu V/10 \text{ dB}$, $P=0.39$), although the majority of patients showed improvement. The conclusion is that beta blockers show a significant decrease in intensity of migraine, especially when combined with a B vitamin like B12 (riboflavin). The use of beta blockers shows strong efficacy without increasing central nervous system side effects in use as a migraine preventative.

**Antidepressants**

Tricyclic antidepressants are the top choice in migraine prophylaxis over SSRIs, SNRIs and MAOIs likely because of their low cost and availability. In limited clinical trials, amitriptyline was shown to work as well as propanolol as an effective treatment for migraines (Silberstein) with medication overuse, insomnia, tension type headache and migraine with depression (Miller). The second option for antidepressant treatment is a selective serotonin reuptake inhibitor which can help alleviate comorbid depression in migraineurs although there is no proof of the efficacy of this route (Ozyalcin). Other antidepressants such as venlafaxine, a serotonin-norepinephrine reuptake inhibitor has proven more effective than placebo in reducing the frequency of attacks in dosages of 150mg (Chronicle).

**Anti-Epileptics (AEDs)**

A Cochrane Review of AEDs showed that migraineurs were more than twice as likely to experience a 50% reduction in the frequency of their migraines versus placebo (Bussone). This includes drugs like valproate, topiramate and gabapentin. Topiramate is a sulfamate-substituted monosaccharide, related to fructose. It is rapidly absorbed (peak plasma concentrations about 2 hours after intake) with a high bioavailability (81% to 95%) (May). Topiramate may not have an impact on a specific channel or subtype, rather, it has effects on multiple channel types. It is known to block voltage gated-ion dependent sodium channels and calcium channels (Zona) and inhibits excitatory glutamate pathway while at the same time enhancing inhibition of GABA and carbonic anhydrase activity (Shank). Valproate shows similar modes of action and is often preferred for patients with comorbid depression or bipolar. Gabapentin is shown to be less efficacious than topiramate and valproate (Miller). The mode of action of these drugs in the role of migraine pathophysiology is still unclear.

**CGRP antagonist**

A young but promising class of drugs used to prevent migraine are calcitonin gene-related peptide antagonists developed as antibodies to block calcitonin receptors in the central nervous system. CGRP influences neuronal modulation of pain and vascular activity. They are found throughout the body but in the pathophysiology of migraine, they are facilitated particular in the dorsal root and trigeminal ganglions (Edvinsson). Two subsets of CGRP therapies exist. Known pharmacologically as “-gepants” (Hershey), the first is a CGRP antagonist, inhibiting the production of CGRP in the dorsal root and trigeminal ganglions. Four monoclonal antibodies (erenumab) are developed to target CGRP receptor (erenumab) or targeting these peptides directly (eptinezumab, fremanezumab and galancanezumab). In phase 3 clinical trials, fremanezumab groups reduced baseline number of migraine attacks by more than two greater than placebo, showing marginal but meaningful efficacy (Hershey). It is relevant to include that...
CGRPs are found throughout the body and their exact function is not understood. The alteration of long term interactions of CGRP antagonists with organ systems is unknown.

**Conclusion**

Since the original characterizations of typical migraine from the eras of Hippocrates to Aretaeus of Cappadocia to Harold G. Wolff and beyond, we now know much more about the pathophysiology and clinical symptoms with key players in their respective roles. Despite the efforts of current research, the complexity of the disorder continues to be just as prevalent issue as anemia and hearing loss in our modern world. Understanding the detriment that this disorder can have on the individual is something that employers, employees, family members and others need to be aware of in order to accommodate for lost time and participation when a migraine attack occurs. The goal of this review was to compile information to help with understanding the major parts involved with the disorder and what can be done to better treat it. The best conclusion to be made is that no one drug may be the end-all answer for every individual. The goal is that one day genetic therapies could conduct target gene therapies for polymorphisms identified in familial migraine symptoms to potentially deal with the gene expression level. More studies in the areas of gut-brain axis may eventually paint a picture of the overall interactions of neuromodulatory peptides and other roles of the peripheral nervous system in migraine disorder.
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