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Key Inforbits

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June is…

MIGRAINE AWARENESS MONTH

About Migraines[1]

Migraines are attacks of moderate-to-severe throbbing headache with associated symptoms that may include nausea, vomiting, and photophobia (intolerance to light) or phonophobia (intolerance to loud sounds). In women 17.1% and 5.6% of men in the United States experience at least one migraine headache per year. Females usually experience their first migraine headache between the ages of 12 and 17, while males' first experience is usually between the ages of 5 and 11 years. These migraine attacks range in severity, but 93% of patients have migraines which cause some disability, and 54% of patients report severe disability from their migraine attack. According to a 2014 study, the mental and social burden is higher among sufferers of migraine than patients with epilepsy, stroke, multiple sclerosis, and Parkinson's Disease.[2] It is estimated that each year Americans spend over $1 billion on migraine diagnosis and/or treatment.

The mechanisms responsible for causing a migraine attack are not completely understood. However, it is believed that the pain is a result from activity within the brain's trigeminovascular system, a network of visceral afferent fibers that arises from the trigeminal ganglia and projects peripherally to innervate the pain-sensitive intracranial extracerebral blood vessels, dura mater, and large venous sinuses. Activation of this system triggers the release of neuropeptides, including calcitonin gene-related peptide (CGRP), neurokinin A, and substance P that promote vasodilation and inflammation of the blood vessels in the brain causing pain. Other proposed causes for migraine headaches include imbalances in electrolytes such as magnesium and potassium or neurotransmitters such as dopamine, glutamate, or serotonin.

Some patients' migraines may be "triggered" by environmental factors. The following is a partial list of potential "triggers" for the onset of a migraine headache:

Common Triggers of Migraines

- **Glare or flickering lights**
- **High altitudes**
- **Loud noises**
- **Strong smells and fumes**
- **Weather changes**
- **Food (i.e. caffeine, chocolate, alcohol, artificial sweeteners)**
- **Insufficient sleep**
- **Skipped meals**
- **Stress**
- **Changes in hormone levels in women (especially during menstruation)**

References:

1. Minor DS, Wofford MR. Headache disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 9th ed. New York: McGraw-Hill Medical; c2014. p. 943-58.
2. Leonardi M. Higher burden of migraine compared to other neurological conditions: results from a cross-sectional study. Neurol Sci [Internet]. 2014[cited 2014 May 30];35(Suppl 1):S149-S152. Available from: http://download.springer.com/static/pdf/402/art%253A10.1007%252Fs10072-014-1780-y.pdf?auth66=1401659089_cf27ab4a121a099f62cc4a40b91b8bb9&ext=.pdf

Clinical Presentation[1]

Symptoms

Migraines are characterized by repeating episodes of throbbing head pain, which are usually unilateral. Migraine pain is usually gradual in onset, peaking in intensity over a period of minutes to hours and lasting between 4-72hrs. Migraine pain is usually reported as moderate-severe and may be associated with nausea (90%) and vomiting (about 33%), as well as sensitivity to light, sound, and/or movement. It should be noted that not all of these symptoms are present during every attack. Once headache pain wanes, patients may experience a resolution phase characterized by feeling tired, exhausted, or irritable.

Diagnosis

Migraine with Aura (Classic Migraine)	• **Aura is defined as symptoms that precede or accompany an attack that evolves over 5-20 minutes and lasts less than 60 minutes. The actual migraine occurs within an hour of the end of the aura. Symptoms usually consist of visual disturbances that affect half ones visual field (flashes of light, spots, or blind spots). The aura may also include tingling/numbness of arms and face, weakness, and/or trouble speaking.** • **Diagnosis:** o Must have had at least 2 attacks o Aura is present o Migraine is not caused by another medical disorder
Migraine without Aura	• Diagnosis: o Must have had at least 5 attacks o Headache attack that lasts 4-72hrs (untreated or unsuccessfully treated) o Must have 2 of the following characteristics: ▪ Unilateral, throbbing pain, moderate-severe intensity or aggravation by routine physical activity (walking, climbing stairs) o During headache must have one of the following: ▪ Nausea or vomiting ▪ Sensitivity to light or noise ▪ Migraine is not caused by another medical disorder

Differential Diagnosis

Tension Headache	• Pain is usually mild-to-moderate, bilateral, and dull nonpulsatile pressure • Disability associated with tension-type is minor compared to migraine • Routine physical activity doesn't affect headache severity • Aura is absent
Cluster Headache	• Most severe of the headache disorders • Hallmark sign: circadian rhythm of painful attacks (attacks occur more at night) • Episodic in 80% of patients o Attacks occur daily for 2 weeks to months, followed by long pain free intervals • Attacks occur suddenly and pain peaks quickly after onset and can last 15-180min. Pain is excruciating, penetrating, and unilateral • No aura and patients generally rock or pace around the room instead of seeking quiet, dark rooms

References:

1) Minor DS, Wofford MR. Headache disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 9th ed. New York: McGraw-Hill Medical; c2014. p. 943-58.

Migraine Management

Living with migraine headaches can be debilitating for not only the patient experiencing them, but also to the patients family, friends, and even employers. As a result, it is increasingly imperative to gain control of both acute migraine attacks and their prevention. It is important that the clinician grasps a clear understanding of the type, severity, and headache-related disability. This understanding will guide decisions for therapy.

Prevention:[1]

Migraines that produce significant disability despite acute therapy, recurring migraines, and increased use of acute therapy are some of the characteristics that may indicate the need for prophylactic therapy. The 2012 Guidelines for Prevention of Episodic Migraine serves as an update to the 2000 guidelines provided by American Headache Society (AHS) and the American Academy of Neurology (AAN). This update differed from the previous guidelines in that it was based entirely on the assessments of the strength of evidence of drug efficacy. It did not address each medications adverse effect profile or current clinical use, which are both necessary when trying to discover the optimum regimen for the patient. Note: Although localized injections of botulinum toxin (Botox injections) have been studied in the prophylaxis of chronic migraines this concept was not addressed in the AHS/AAN guidelines. Results from studies have not produced consistent, statistically significant improvements in the relief of such migraines. Further supporting data is essential to identify its therapeutic use and should only be considered in those patients that are not able to tolerate oral therapy due to associated adverse effects. The following chart summarizes the panel's recommendations.

2012 Guidelines for Prevention of Episodic Migraine Summary

Strength of Evidence	Panel's Recommendation	Medications
Level A: Established as effective	*Should be offered* to patients requiring migraine prophylaxis	Divalproex/sodium valproate, Metoprolol, Propranolol, Timolol, Topiramate, Petasites (butterbur)
Level B: Probably effective	*Should be considered* for patients requiring migraine prophylaxis	Amitriptyline, Venlafaxine, Atenolol Fenoprofen, Ketoprofen, Ibuprofen, Naproxen
Level C: Possibly effective	*May be considered* for patients requiring migraine prophylaxis	Carbamazepine, Clonidine, Candesartan, Lisinopril, Nebivolol

Adapted from: Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012 Apr 24; 78: 1337-1345

Acute Treatment: [2,3]

Rapid resolution of the attack is the primary goal for an acute migraine attack. Additionally, limiting the amount of medication use is equally important. Frequent or excessive use of these medications has the potential to cause a paradoxical increase in migraine and/or headache frequency. This is termed as medication-overuse headache and greatly contributes to repeated attacks. Pharmacologic therapy for the acute migraines includes over-the-counter medications, as well as, various classes and dosage forms of prescription medications. Preference to which therapy should be used remains controversial among clinicians and ultimately depends on patient preference.

Treatment	Clinical Use
Analgesics and Non-steroidal anti-inflammatory drugs (NSAIDs) *Acetaminophen or Aspirin ± Butalbital/Caffeine, Ibuprofen, Naproxen, Diclofenac*	• Reasonable first-line choice for mild-to-moderate attacks • Combination of these increases efficacy and often decreases adverse effects • NSAIDs should be used cautiously in patients with previous renal or ulcer disease • Benefits: majority are available OTC
Serotonin Receptor Antagonists (Triptans) *Sumatriptan (first generation), Zolmitriptan, Naratriptan, Rizatriptan, Almotriptan, Frovatriptan, Eletriptan*	• Appropriate first-line therapy for patients with mild-to-severe migraines • Can be used as rescue therapy; reduce nausea and light sensitivity • Broad onset of action and duration • Mild-to-moderate adverse effects • Benefits: multiple dosage forms (oral tablets, ODT, injections, nasal sprays)
Opiate Analgesics *Oxycodone, Hydromorphone, Meperidine, Butorphanol*	• Effective; reserve for patients with moderate-to-severe infrequent migraines with a failed response to conventional therapies • Caution: rebound headache and/or opioid dependency
Ergot Alkaloids *Ergotamine tartrate, Dihydroergotamine*	• Considered for the treatment of moderate-to-severe migraines • Most effective when administered early in attack • Benefits: available in multiple dosage forms • Nausea and vomiting
Antiemetics *Metoclopramide, Prochloperazine*	• Adjunct therapy for nausea and vomiting associated with migraines

References:

1.) Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012 Apr 24; 78: 1337-1345.

2.) Minor DS, Wofford MR. Headache disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 9th ed. New York: McGraw-Hill Medical; c2014. p. 943-58.

3.) National headache foundation [Internet]. New Orleans: National Headache Foundation; c2014. Standards of care for headache diagnosis and treatment; 2014 [cited 2014 May 28]; [about 5 screens]. Available from: http://www.headaches.org/content/standards-care-headache-diagnosis-and-treatment

Recent Developments

The FDA has just recently approved a device called the Cerena Transcranial Magnetic Stimulator (Cerena TMS). This is the first device that has been proven to relieve pain caused by migraine headaches that are preceded by aura. About one third of people with migraines experience aura indicating that there is a large population for this product. The device is hand held and placed behind the back of the head. The user presses a button, which releases a pulse of magnetic energy to stimulate the occipital cortex of the brain, which is intended to stop or lessen the pain of the migraine. This product was approved after analysis of 201 patients who experienced migraine with aura at least 30% of the time; 113 of the patients reported using the device for treatment of their migraine pain. Of these patients, 38% were pain free within 2 hours after using the device compared to 17% of patients who didn't use the device. After 24 hours, nearly 34 percent of Cerena TMS users were pain free compared to 10% of non Cerena TMS users. The study did not however show that the device relieved aura symptoms (light or sound sensitivity). Also, the study did not evaluate the device's effectiveness in migraine without aura. The device is prescription only, must be 18 years of age for use, and the daily usage may not exceed one treatment in 24 hours.[1]

Studies were presented at this years' American Academy of Neurology's annual meeting that there may be two new drugs that may prevent migraines. Dr. Peter Goadsby, who is the co–author of both studies, stated that these new drugs (ALD403, LY2951742) use a different mechanism to reduce frequency, number, and severity of attacks of migraines. This new mechanism blocks the calcitonin gene related peptide (CGRP), which is one of the key chemicals that causes the debilitating effects of migraines. Blocking the CGRP stops the migraine from starting. This is exciting news because according to the Mayo Clinic there has not been a new drug targeting the prevention of migraines in the past 50 years. All the drugs currently on the market for prevention of migraines are indicated for other disease states (eg. topiramate for epilepsy). Goadsby stated that since these drugs are targeting a specific cause of migraines they should lead to fewer side effects as compared to the other preventative drugs that were designed to treat another disease. The issue is there is a lack of funding for the products, which is a common theme in migraine research. The drugs still need to be tested in large scale clinical trials and receive FDA approval before patient access can be achieved. Researchers estimate that approval may be at least 3 years away.[2]

References:

1) FDA: FDA news release [Internet] FDA allows marketing of first device to relieve migraine headache pain; 2013 Dec13 [cited 2014 May 30]; [about 2 screens]. Available from: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm378608.htm
2) CNN: Health [Internet] New migraine treatments show promise; 2014 Apr 22 [cited 2014 May 30]; [about 3 screens]. Available from: http://thechart.blogs.cnn.com/2014/04/22/new-migraine-treatments-show-promise/

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