Migraine

Migraine, a common, recurrent, primary headache of moderate to severe intensity, interferes with normal functioning and is associated with gastrointestinal, neurologic and autonomic symptoms. In migraine with aura, focal neurologic symptoms precede or accompany the attack.

Activation of trigeminal sensory nerves triggers the release of vasoactive neuropeptides, including calcitonin gene-related peptide, neurokinin A and substance P from perivascular axons. Vasodilation of dural blood vessels may occur with extravasation of dural plasma resulting in inflammation.

Studies suggest 50% heritability of migraine, with a multifactorial polygenic basis. Migraine triggers may be modulators of the genetic set point that predisposes to migraine headache.

Specific populations of serotonin (5-HT) receptors appear to be involved in the pathophysiology and treatment of migraine headache. Ergot alkaloids and triptan derivatives are agonists of vascular and neuronal 5-HT_1 receptors, resulting in vasoconstriction and inhibition of vasoactive neuropeptide release.

Clinical presentation and diagnosis

Migraine headache is characterized by recurring episodes of throbbing head pain, frequently unilateral.

Approximately 12% to 79% of patients with migraine (=migraineurs) have ***premonitory symptoms*** (*prodrome*) in the hours or days before headache onset.

Migraine headache may occur at any time but usually occurs in the early morning. Pain is usually gradual in onset, peaking in intensity over minutes to hours and lasting 4 to 72 hours. Pain is typically in the frontotemporal region and is moderate to severe. Headache is usually unilateral throbbing.

Other symptoms include:

- *Neurologic symptoms* (phonophobia, photophobia, hyperosmia, and difficulty concentrating)
- *Psychological symptoms* (anxiety, depression, euphoria, irritability, drowsiness, hyperactivity and restlessness)
- *Autonomic symptoms* (e.g., polyuria, diarrhea and constipation)
- *Constitutional symptoms* (e.g., stiff neck, yawning, thirst, food cravings and anorexia).

- A migraine ***aura*** is experienced by approximately 25% of migraineurs. Aura evolves over 5 to 20 minutes and lasts less than 60 minutes. Headache usually occurs within 60 minutes of the end of the aura. ***Visual auras*** can include both positive features (e.g., scintillations, photopsia, teichopsia, and fortification spectrum) and negative features (e.g., scotoma and hemianopsia).
- *Sensory and motor symptoms* such as paresthesias or numbness of the arms and face, dysphasia or aphasia, weakness, and hemiparesis may also occur.
- *GI symptoms* (e.g., nausea and vomiting in addition to anorexia, constipation, diarrhea and abdominal cramps).
- *Sensory hyperacuity* (photophobia, phonophobia, or osmophobia) is frequent. Many patients seek a dark, quiet place.
- Other systemic symptoms include nasal stuffiness, blurred vision, diaphoresis, facial pallor, and localized facial, scalp or periorbital edema.

Once the headache pain wanes, a ***resolution phase*** (*postdrome*) characterized by exhaustion, malaise, and irritability ensues.

A comprehensive headache history is essential and includes age at onset; frequency, timing, and duration of attacks; possible triggers; ameliorating factors; description and characteristics of symptoms; associated signs and symptoms; treatment history; and family and social history.

Neuroimaging should be considered in patients with unexplained abnormal neurologic examination or atypical headache history.

Onset of migraine headaches after age 50 suggests an organic etiology, such as a mass lesion, cerebrovascular disease or temporal arteritis.

Triggers of Migraine

1. Food triggers
   - Alcohol
   - Caffeine/caffeine withdrawal
   - Chocolate
   - Fermented and pickled foods
   - Monosodium glutamate (e.g., in Chinese food, seasoned salt, and instant foods)
   - Nitrate-containing foods (e.g., processed meats)
   - Saccharin/aspartame (e.g., diet foods or diet sodas)
   - Tyramine-containing foods

2. Environmental triggers
   - Glare or flickering lights
   - High altitude
   - Loud noises
   - Strong smells and fumes
   - Tobacco smoke
   - Weather changes
3. Behavioral–physiologic triggers
   - Excess or insufficient sleep
   - Fatigue
   - Menstruation, menopause
   - Sexual activity
   - Skipped meals
   - Strenuous physical activity (e.g., prolonged overexertion)
   - Stress or post stress

Treatment

Pharmacologic agents used for the treatment of migraine can be classified as abortive (i.e., for alleviating the acute phase) or prophylactic (i.e., preventive). The goal is to achieve consistent, rapid headache relief with minimal adverse effects and symptom recurrence, and minimal disability and emotional distress.

It is recommended to limit use of acute migraine therapies to avoid development of medication-misuse headache.

Non-pharmacologic Treatment

Non-pharmacologic treatment includes:

- Ice application to the head and periods of rest or sleep.
- Identification triggers of migraine to avoid them.
- Behavioral interventions (relaxation, biofeedback and cognitive therapy)

Pharmacologic Treatment of Acute Migraine

- An acute migraine therapy should be used at the onset of migraine.
- Pretreatment with an ***antiemetic*** (e.g., metoclopramide, chlorpromazine, or prochlorperazine) 15 to 30 minutes before oral or non-oral migraine treatments (rectal suppositories, nasal spray, or injections) may be advisable when nausea and vomiting are severe. In addition to its antiemetic effects, ***metoclopramide*** helps reverse gastroparesis and enhances absorption of oral medications.

- Frequent or excessive use of acute migraine medications can result in increasing headache frequency and drug consumption known as ***medication-overuse headache***.

✓ ***Analgesics and nonsteroidal antiinflammatory drugs***

Simple analgesics and NSAIDs are first-line treatments for mild to moderate migraine attacks; some severe attacks are also responsive. Aspirin, diclofenac, ibuprofen, ketorolac, naproxen sodium, tolfenamic acid, and the combination of acetaminophen plus aspirin and caffeine or butalbital are effective.

In case of nausea and vomiting, rectal and IM routes are considered to administer NSAIDs.

✓ ***Ergot alkaloids and derivatives***

- Ergot alkaloids are useful for moderate to severe migraine attacks. They are nonselective $5HT_1$ receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system. Venous and arterial constriction occurs. They also have activity at dopaminergic receptors.
- ***Ergotamine tartrate*** is available for oral, sublingual, and rectal administration. Oral and rectal preparations contain ***caffeine*** to enhance absorption and potentiate analgesia.
- ***Dihydroergotamine*** is available for intranasal and parenteral (IM, IV or SC) administration.
- Nausea and vomiting are common with ergotamine derivatives, so they are better to be used with antiemetic pretreatment. Use of ergotamine derivatives and triptans within 24 hours should be avoided.
- Contraindications to use of ergot derivatives include renal and hepatic failure; coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; sepsis; and women who are pregnant or nursing.

✓ ***Serotonin receptor agonists (triptans)***

- The triptans are appropriate first-line therapies for patients with mild to severe migraine or as rescue therapy when nonspecific medications are ineffective.
- ***Sumatriptan*** is available in oral and intranasal formulations and SC injection.
- Second-generation triptans (*frovatriptan, naratriptan, zolmitriptan, almotriptan, Eletriptan and rizatriptan*) have higher oral bioavailability and longer half-lives than oral sumatriptan, which could theoretically reduce headache recurrence.

- Lack of response to one triptan does not preclude effective therapy with another triptan.
- Contraindications include ischemic heart disease, uncontrolled hypertension, cerebrovascular disease, hemiplegic and basilar migraine, and pregnancy.
- A cardiovascular assessment should be done before giving triptans to postmenopausal women, men over 40 years of age, and patients with uncontrolled risk factors. First dose should be administered under medical supervision.
- Ergot alkaloids and triptans should not be used concomitantly. A 24 hours' period is the minimum period to switch to the other agent.

✓ ***Opioids***

Opioids and derivatives (e.g., meperidine, butorphanol, oxycodone, and hydromorphone) are reserved for patients with moderate to severe infrequent headaches in whom conventional therapies are contraindicated or as rescue medication after failure to respond to conventional therapies.

Pharmacologic Prophylaxis of Migraine

- Prophylactic therapies are administered daily to reduce the frequency, severity and duration of attacks, and to increase responsiveness to acute therapies.
- Prophylactic therapy is indicated in cases:
    - Recurring migraines that produce significant disability
    - Frequent attacks requiring symptomatic medication more than twice per week
    - Symptomatic therapies that are ineffective, contraindicated, or produce serious side effects
    - Uncommon migraine variants that cause profound disruption or risk of neurologic injury
    - Patient preference to limit the number of attacks.
- Preventive therapy may also be given intermittently when headaches recur in a predictable pattern (e.g., exercise-induced or menstrual migraine).
- Only ***propranolol***, ***timolol***, ***divalproex sodium***, and ***topiramate*** are Food and Drug Administration (FDA) approved for migraine prevention.
- Prophylactic therapy continues for at least 6 to 12 months after headache frequency and severity have diminished, and then gradual tapering or discontinuation may be reasonable.

✓ ***Antidepressants***

- The ***tricyclic antidepressants*** (TCA) *amitriptyline* and *venlafaxine* are probably effective for migraine prophylaxis. There are insufficient data to support or refute the efficacy of other antidepressants.
- Their beneficial effects in migraine prophylaxis are independent of antidepressant activity.
- TCAs are usually well tolerated at the doses used for migraine prophylaxis, but anticholinergic effects may limit use, especially in elderly patients or those with benign prostatic hyperplasia or glaucoma. Evening doses are preferred because of sedation.
- ***SSRIs*** have limited efficacy for migraine prophylaxis in adults. Due to a lack of clinical studies, they are not recommended for this purpose in children.

✓ ***Serotonin receptor agonists (triptans)***

Serotonin 5-HT receptor agonists or Triptans (***frovatriptan***, naratriptan and zolmitriptan) may be used in prophylaxis of menstrual migraine.

✓ ***B-adrenergic antagonists***

- ***Propranolol***, *timolol* and *metoprolol* reduce the frequency of migraine attacks. *Atenolol* and *nadolol* are probably also effective.
- β-Blockers with intrinsic sympathomimetic activity (*oxprenolol, pindolol, penbutolol, labetalol and acebutolol*) are ineffective.

✓ ***Anticonvulsants***

- *Valproic acid*, *divalproex sodium* and ***topiramate*** can reduce the frequency, severity and duration of headaches.
- Side effects of valproic acid and divalproex sodium include nausea, tremor, somnolence, weight gain, hair loss, and hepatotoxicity.
- 50% of patients respond to topiramate. Paresthesias and weight loss are common side effects.

✓ ***Nonsteroidal antiinflammatory drugs***

- NSAIDs are modestly effective for reducing the frequency, severity and duration of migraine attacks. Evidence for efficacy is strongest for naproxen and weakest for aspirin.
- They may be used intermittently to prevent headaches that recur in a predictable pattern (e.g., menstrual migraine). Treatment should be initiated 1 or 2 days before the time of headache vulnerability and continued until vulnerability is passed.

✓ ***Anti-CGRP agents***

- Calcitonin gene-related peptide (CGRP) is a potent vasodilator and is a key neuropeptide that is central to migraine pathophysiology. ***Anti-CGRP agents*** were developed. They are indicated for preventive treatment of migraines in adults.
- Erenumab is CGRP-receptor antagonists. It was approved by FDA and EMA in 2017.
- Fremanezumab and galcanezumab were approved by FDA in September 2018. They are antagonists of CGRP molecule.

✓ ***Calcium channel blockers***

- ***Calcium channel blockers*** are commonly used as prophylactic medication for migraine. Flunarizine has the best-documented efficacy. Verapamil has been widely used and supported by studies, but evidence for efficacy is inadequate.

✓ ***Botulinum toxin A***

- Injections of ***OnabotulinumtoxinA*** (Botox) may be beneficial in patients with intractable migraine headaches that fail to respond to at least 3 conventional preventive medications. This agent is not recommended for use in the preventive treatment of episodic migraines.

✓ ***Herbal products***

- ***Petasites*** (butterbur) is established as effective and the guideline highly recommend it for migraine prevention.

Tension-type headache

- Tension-type headache, the most common type of primary headache, is more common in women than men. Pain is usually mild to moderate and nonpulsatile. Episodic headaches may become chronic in some patients.
- Premonitory symptoms and aura are absent, and pain is usually mild to moderate, bilateral, nonpulsatile, and in the frontal and temporal areas, but occipital and parietal areas can also be affected.
- Mild photophobia or phonophobia may occur. Pericranial or cervical muscles may have tender spots or localized nodules in some patients.

Treatment

- Non-pharmacologic therapies include reassurance and counseling, stress management, relaxation training and biofeedback. Physical therapeutic options (e.g., heat or cold packs, ultrasound, electrical nerve stimulation, massage, acupuncture, trigger point injections, and occipital nerve blocks) have performed inconsistently.
- Simple analgesics such as paracetamol (alone or in combination with caffeine or butalbital) and NSAIDs (such as aspirin, diclofenac, ibuprofen, naproxen, ketoprofen and ketorolac) are the mainstay of acute therapy.
- A preventive treatment is to be considered if headache frequency is more than two per week, duration is longer than 3 to 4 hours or severity results in medication overuse or substantial disability.
- The TCAs are used most often for prophylaxis of tension headache, but venlafaxine, mirtazapine, gabapentin, topiramate and tizanidine may also be effective.