

Migraine, Tension, and Cluster Headache: Primary Care for Primary Headaches

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Learning objectives

1. Utilize evidence-based strategies to diagnose patients presenting with headache.
2. Identify associated conditions (e.g. depression), and red flags for potentially life threatening causes of headache.
3. Use evidence-based recommendations to prescribe treatment for patients presenting with acute or emergent headache pain.
4. Develop collaborate management plans, emphasizing patient education on avoiding triggers that cause headache, and adherence to prescribed treatment strategies.

Headache

- References to headache can be found in the Ebers Papyrus (1200 B.C.)
- Evidence of trepanation of 9000 year old Neolithic skulls suggests early headache treatment
- Lifetime prevalence: 96%
- Direct and indirect socioeconomic costs estimated at \$14 billion annually

Tension headache

Tension headache: basics

- Lifetime prevalence in general population:
30-78%, depending on study
- Episodic (infrequent and frequent) and chronic

Tension frequency

Infrequent episodic:

- At least 10 episodes of a headache occurring on <1 day per month on average (<12 days per year)

Frequent episodic:

- At least 10 episodes of headache occurring on 1-14 days per month on average for >3 months (≥ 12 and <180 days per year)

Tension headache: diagnosis

B. Lasting from 30 minutes to 7 days

C. At least two of the following four characteristics:

1. bilateral location
2. pressing or tightening (non-pulsating) quality
3. mild or moderate intensity
4. not aggravated by routine physical activity such as walking or climbing stairs

D. Both of the following: 1. no nausea or vomiting 2. no more than one of photophobia or phonophobia

Tension headache: treatment

- Limited evidence base to support specific treatments
- Consider:
 - Acetaminophen
 - NSAIDs: short-acting (e.g. ibuprofen, diclofenac, naproxyn sodium) tend to have better efficacy
- Less preferable:
 - Combination medications containing caffeine
 - Narcotic analgesics, barbiturates

Cluster headache

Trigeminal autonomic cephalgias

3.1 Cluster headache

3.1.1 Episodic cluster headache

3.1.2 Chronic cluster headache

3.2 Paroxysmal hemicrania

3.2.1 Episodic paroxysmal hemicrania

3.2.2 Chronic paroxysmal hemicrania

3.3 Short-lasting unilateral neuralgiform headache attacks

3.4 Hemicrania continua

3.5 Probable trigeminal autonomic cephalalgia

Cluster headache: the basics

- Most common of the trigeminal autonomic cephalalgias
- Lifetime prevalence > 1 per 1000
- Not easily recognized, which leads to diagnostic delay
- Age at onset typically 20-40 years
- Male : female = 3:1
- Attacks may be provoked by alcohol, histamine, nitroglycerin

Cluster headache: the basics

- Autosomal dominant in approximately 5% of cases
- Attacks occur in series/clusters lasting for weeks or months, separated by remission period of months or years
- 10-15% have chronic cluster headache without remission periods
- Approximately 25% have only one cluster period

Cluster headache: diagnosis

A. At least five attacks fulfilling criteria B–D

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)

Cluster headache: diagnosis

- C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
 - a) conjunctival injection and/or lacrimation
 - b) nasal congestion and/or rhinorrhea
 - c) eyelid edema
 - d) forehead and facial sweating
 - e) forehead and facial flushing
 - f) sensation of fullness in the ear
 - g) miosis and/or ptosis
 2. a sense of restlessness or agitation

Cluster headache: diagnosis

D. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active

E. Not better accounted for by another ICHD-3 diagnosis.

Cluster headache: treatment

- Established as effective:
 - Sumatriptan (subcutaneous; 6 mg)
 - Zolmitriptan (nasal spray; 5 and 10 mg)
 - Oxygen (100%; 6-12 L/min flow)

Cluster headache: treatment

- Probably effective:
 - Sumatriptan (nasal spray; 20 mg)
 - Zolmitriptan (oral; 5 and 10 mg)
 - Sphenopalatine ganglion stimulation

Cluster headache: treatment

- Possibly effective:
 - Cocaine/lidocaine (nasal spray; 10% each)
 - Octreotide (subcutaneous; 100 mcg)
- Insufficient evidence:
 - Dihydroergotamine (nasal spray; 1 mg)
 - Somatostatin
 - Prednisone

Cluster headache: prophylaxis

- Established as effective:
 - Suboccipital steroid injection
- Possibly effective:
 - Lithium (oral; 900 mg daily)
 - Verapamil (oral; 360 mg daily)
 - Melatonin (oral; 10 mg every evening)
 - Warfarin (oral; target INR 1.5-1.9)

Migraine headache

Migraine: basics

- Approximately 12% of the general population affected
- Female : male = 3:1
- Approximately one-third of patients have an initial aura of neurological symptoms, most often a visual scotoma
- Lifetime prevalence is at least 18%
- Most common in patients aged 30-39
- Family history of migraine is seen in at least 50% of migraine patients

Migraine: pathophysiology

- A neurovascular headache:
 - Neural events trigger dilation of blood vessels, resulting in pain and further nerve activation
 - Aura is characterized by a short phase of hyperemia, followed by a wave of oligemia or spreading depression that passes across the cortex at 2-6mm/min

Migraine: pathophysiology

- Trigeminal nerve activation occurs
 - Referred pain in the parietal, occipital and high cervical regions
- If treatment is delayed or ineffective, central sensitization may occur with associated cutaneous allodynia

Important historical questions

- Age at onset
- Presence or absence of aura and prodrome
- Frequency, intensity and duration of attack
- Number of headache days per month
- Time and mode of onset
- Associated symptoms and abnormalities
- Family history of migraine
- Quality, site, and radiation of pain
- Precipitating and relieving factors

Important historical questions

- Effect of activity on pain
- Relationship with food/alcohol
- Response to any previous treatment
- Any recent change in vision
- Association with recent trauma
- State of general health
- Any recent changes in sleep, exercise, weight, or diet
- Change in work or lifestyle (disability)
- Change in method of birth control (women)
- Possible association with environmental factors
- Effects of menstrual cycle and exogenous hormones

Four questions from the American Association of Neurology

1. How often do you get severe headaches (i.e., without treatment it is difficult to function)?
2. How often do you get other (milder) headaches?
3. How often do you take headache relievers or pain pills?
4. Has there been any recent change in your headaches?

Accuracy of four-question approach

- In one validation study, the presence of *episodic disabling headache* correctly identified migraine in 136 of 146 patients (93 percent) with episodic migraine, and 154 of 197 patients (78 percent) with chronic headache with migraine, with a specificity of 63 percent.
- Only 6 of 343 patients (1.7 percent) with migraine were not identified by disabling headache.

Migraine: diagnosis

- A. At least five attacks fulfilling criteria B–D

- E. Not better accounted for by another ICHD-3 diagnosis.

Migraine: diagnosis

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

Other potential features

- Vascular changes: cold hands and feet, tenderness over the superficial vessels where the headache occurs, pale skin of face
- Weight increase, Na⁺ retention, oliguria
- Hyperesthesia of scalp

Other potential features

Trigeminal activation may also cause:

- Nasal congestion
- Rhinorrhea
- Lacrimation
- Facial pain, especially in maxillary region
- Tooth pain, especially maxillary

Prodrome

- Premonitory symptoms occur in migraine with and without aura, and may precede headache by up to 24 hours; present in up to 60% of patients
 - Mood changes: depression, hyperactivity, irritability, euphoria
 - Increased appetite / food cravings
 - Excessive yawning, fatigue
 - Neck stiffness/pain

Aura

- Aura occurs in about 35% of migraines
 - Typically precedes attack by 15-30 minutes
 - Not every patient who has migraine with aura has aura with every headache
- Negative visual: Scotomata, or blind spots
- Positive visual: Scintillations
- Paresthesias
- Visual and auditory hallucinations

Postdrome

- A sort of “post-ictal” phase, which may last hours to a day or more
- Na^+ retention and oliguria reverse with subsequent diuresis
- Many patients report a period when they are refractory to subsequent migraine

Migraine and cardiovascular risk

Physicians' Health Study

- Prospective cohort study of 40-84 year old male physicians
- The 7.2% who self-reported migraine had multivariable-adjusted hazard ratios of 1.24 for major CVD, 1.42 for myocardial infarction
- Age-adjusted HR for ischemic stroke was 1.84 in men <55 years; no significant association in older age groups
- Information on aura was not recorded, nor was information about use of migraine-specific drugs

Migraine and cardiovascular risk

Nurses' Health Study II

- 115,541 women aged 25-42 years at baseline and free of angina and cardiovascular disease
- Cumulative follow-up rates were more than 90%
- 17,531 (15.2%) women reported a physician's diagnosis of migraine

Migraine and cardiovascular risk

After adjustment for potential confounding factors, migraine was associated with an increased risk for:

- major cardiovascular disease
(HR 1.50; 95% CI 1.33 to 1.69)
- myocardial infarction (1.39; 1.18 to 1.64)
- stroke (1.62; 1.37 to 1.92)
- angina/coronary revascularization procedures
(1.73; 1.29 to 2.32)
- risk for cardiovascular disease mortality
(HR 1.37; 1.02 to 1.83)

You've got the clinical diagnosis

But doctor, what if I have a brain tumor?

Neuroimaging

- Neuroimaging is not usually warranted for patients with migraine and normal neurologic exam (Grade B)
- Symptoms that significantly increase odds of finding a significant abnormality on neuroimaging:
 - Rapidly increasing headache frequency
 - History of dizziness or lack of coordination
 - History of subjective numbness or tingling
 - History of headache causing awakening from sleep

Neuroimaging: How much to spend?

- MRI may be more sensitive than CT for identifying clinically insignificant abnormalities, but may not be more sensitive for identifying clinically significant pathology that is relevant to the cause of headache

Medication options: NSAIDs

- NSAIDs are reasonable for mild to moderate pain
 - Inhibition of prostaglandin synthesis prevents neurogenically mediated inflammation in the trigeminovascular system
 - May also interfere with serotonin neurotransmission and modulate vasoconstriction

Medication options: Dihydroergotamine

- Differs from ergotamine: less nausea and increased vasoconstrictive effects
- DHE-45: 1mg IM; may repeat hourly up to 3mg daily
- Minimum of 5 days between treatment days
- Also available as a nasal spray (Migranal): 2mg dose, 1 spray in each nostril; repeat in 15min, up to 3mg per day

The triptans

- Serotonin is thought to have a pivotal role in migraine pathogenesis
- 5-HT_{1B/1D} receptor agonists
- Potential mechanisms of action:
 - Normalization of dilated intracranial arteries
 - Peripheral neuronal inhibition
 - Neuronal inhibition of second-order neurons of the trigemino-cervical complex

Triptans: individual characteristics

Sumatriptan (Imitrex): available for longest, most number of dosing forms, given successfully to most number of patients
(oral 25-50mg; nasal 20mg; SQ 6mg)

Zolmitriptan (Zomig): only triptan proven effective when repeated for persistent headache
(oral/ODT 2.5-5mg; nasal 2.5-5mg)

Naratriptan (Amerge): slower onset but favorable adverse event profile and lower recurrence rate
(oral 1-2.5mg)

Triptans: individual characteristics

Rizatriptan (Maxalt): highest 2-hour and sustained pain-free rates, fastest time to response of any oral tablet
(oral/ODT 5-10mg)

Almotriptan (Axert): slightly better adverse event profile, less chest pain than sumatriptan
(oral 12.5mg)

Eletriptan (Relpax): clear dose-response curve, good sustained response rates
(oral 20-40mg)

Frovatriptan (Frova): slower acting, longest half-life in class
(oral 2.5mg)

Despite the individual characteristics...

- Oral triptans within each group are more similar than different
- It is not possible to predict which triptan will work best for any given patient
- Tolerability problems as a reason for discontinuation are relatively rare for all triptans

Triptans: dosing strategies

- Avoid starting with “baby doses”
- Try a med for 2-3 headaches before concluding it’s not effective, unless side effects are the problem
- Rizatriptan (Maxalt) and eletriptan (Axert) tend to offer the best combination of efficacy and tolerability; the other five are excellent choices as well

Migraine: prophylaxis

Should be considered in patients:

- Who experience 2 or more migraines per month
- Whose migraines greatly affect quality of life and ability to function
- For whom abortive therapies have been unsuccessful
- For whom abortive therapies are contraindicated

Migraine prophylaxis: beta-blockers

- Propranolol (80-160mg daily divided or 60-160mg ER) and timolol (5-30mg daily) are FDA-approved
- Metoprolol, atenolol and nebivolol have limited supporting evidence
- Beta-blockers with ISA (intrinsic sympathomimetic activity) have been shown *ineffective* as prophylaxis (oxprenolol, pindolol, penbutolol and acebutolol)

Migraine prophylaxis: antidepressants

- Amitriptyline (50-100mg hs) is the only antidepressant with consistent evidence supporting its effectiveness; it is more beneficial in mixed migraine-tension headache
- While not as well studied, nortriptyline and desipramine are typically better tolerated
- SSRIs consistently demonstrate *no effect* on migraine frequency/severity

Migraine prophylaxis: antiepileptic drugs

- Divalproex sodium
 - Depakote ER: 500mg qhs for 1 week, then increase to 1000mg qhs
 - Side effects may include:
 - Nausea
 - Sedation
 - Appetite increase (transient)
 - Hair thinning

Migraine prophylaxis: antiepileptic drugs

- Topiramate
 - Topamax 25 mg qhs for 1 week, then titrate by 25 mg weekly – either split or hs dosing – to target of 100 mg daily
 - Side effects may include:
 - Paresthesias
 - Appetite decrease
 - Carbonic anhydrase inhibitor

Migraine prophylaxis: antiepileptic drugs

- Doses lower than target may still be effective if tolerability becomes an issue
- Intermittent difficulty with “word finding” is frequently seen with AEDs
- Virtually all AEDs can cause hepatotoxicity and suppression of one or more blood cell line
- Divalproex has a black box warning for hepatotoxicity; LFT monitoring is recommended at baseline and “frequently” for the first 6 months
- Periodic CBC and chemistry is advisable

Migraine prophylaxis: onabotulinumtoxin A

- 155 units IM divided over 7 specific head/neck muscle areas every 12 weeks
- FDA-approved for prevention of chronic migraine (≥ 15 headache days per month with headache lasting 4 hours per day or longer)

Migraine prophylaxis: other drugs

- Weak evidence or efficacy in small trials:
 - Verapamil
 - Lisinopril
 - Candesartan
 - Venlafaxine XR
 - Duloxetine

Feature	Migraine	Tension	Cluster
Location	Unilateral in 60 to 70 percent; bifrontal or global in 30 percent	Bilateral	Always unilateral, typically begins around eye or temple
Characteristics	Gradual in onset, crescendo pattern; pulsating; moderate or severe intensity; aggravated by routine physical activity	Pressure or tightness which waxes and wanes	Pain begins quickly, reaches a crescendo within minutes; pain is deep, continuous, excruciating, and explosive in quality
Pt appearance	Patient prefers to rest in a dark, quiet room	Patient may remain active or may need to rest	Patient remains active
Duration	4 to 72 hours	Variable	30 minutes to 3 hours
Associated symptoms	Nausea, vomiting, photophobia, phonophobia; may have aura (usually visual, but can involve other senses or cause speech or motor deficits)	None	Ipsilateral lacrimation and redness of the eye; stuffy nose; rhinorrhea; pallor; sweating; Horner's syndrome; focal neurologic symptoms rare; sensitivity to alcohol

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