Part I
Classification and Diagnosis

Primary Headaches

<table>
<thead>
<tr>
<th>Prevalence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension headache</td>
<td>78%</td>
</tr>
<tr>
<td>Migraine</td>
<td>20%</td>
</tr>
<tr>
<td>Trigeminal autonomic cephalgias</td>
<td>0.07% (Cluster headache, M:F=6:1)</td>
</tr>
<tr>
<td>Familial hemiplegic migraine</td>
<td>0.0002%</td>
</tr>
<tr>
<td>Chronic daily headache</td>
<td>3-5% (accounts for 70-80% office visits)</td>
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</tbody>
</table>

Secondary Headaches

- SAH
- Infection
  - CNS or systemic
  - Sinus (15%)
- Abnormal ICP
  - Too high
  - Too low
- Intracranial tumors
- Giant Cell Arteritis
- Trauma
- GI
- Hypoxia
- Otitis media
- Intraspinal
- Head trauma
- Pituitary tumor
- Saεrvical root compression
- Intracranial masses
- Increased intracranial pressure

Systemic Causes of Headache

- Giant cell arteritis
- Infections (encephalitis, meningitis, sinusitis)
- Increased PCO2 (COPD, sleep apnoea)
- Mastocytosis
- Pheochromocytoma
- Severe rise in BP
  - >25% of diastolic, or
  - combined systolic and diastolic (~ 180/130)
- Toxins and drugs

Headaches

Primary
- Migraine
- Cluster (TACs)
- Primary stabbing headache (ice pick-like headache)
- Tension-type headache
- SUNCT, SUNA
- Hypnic headache
- Nummular headache

Secondary
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Red Flags for 20 Headache

• First
• Worst
• Abrupt onset
• Precipitated by valsalva – exertion/stooping – collius – sneezing/coughing
• Head or neck injury
• Onset after age 50
• Progressive worsening

• Atypical history
• New onset, or a change in the pattern
• Abnormal findings – Fever, stiff neck – Weight loss, jaw claudication, scalp tenderness, severe HTN, etc.
– Neurological deficit Beware the numb chin/cheek
• Pre-existing risk factors – Immunosuppression, HIV – Hx of cancer
• Poor response to Rx

Yellow Flags for 20 Headache

• Headaches that awaken the patient
– More worrisome in children
• Headache that are always on the same side
• Prominent effect with a change in posture
– Spontaneous intracranial hypotension (SIH)*
– Intraventricular and posterior fossa tumors, Chiari *most common

Circadian Periodicity

Time of onset of 3,328 migraine attacks Fox & Davis. Headache 1998;38:436

Typical Clinic Patient

J.B. A 35 year old computer I.T.
• Hx: Sinus headaches for 10 years – seven severe headaches per month
– last most of day (occasionally up to a week)
– often present on awakening
– painful bifrontal & retro-orbital pressure
– feels congested
• Exam: Normal

A Few Probing Questions Revealed:

• Worse on the left side (predominantly hemicranial)
• Worse with activity
• Nausea when severe
• Difficulty concentrating (cognitive dysfunction)
• Prefers dark quiet room when h/a severe
• Misses work because of headaches
• Feels congested, but no nasal discharge or fever

What Now?
**Outside Sinus CT**

![Sinus CT images]

**Diagnosis**

**MIGRAINE**

**Migraine**

- Migraine is the most common form of headache provoking patients to seek help
- Migraine is frequently misdiagnosed as either “sinus” or tension-type headache
- True sinus headache is uncommon
- Tension type headache is rarely severe enough to warrant a visit to the doctor

**Migraine was not recognized:**

Because he had:

- no warning (aura)
- no visual symptoms of any kind
- no vomiting
- no family history of migraine or “sick headaches”

**Acute Sinus Headache**

*ICHD-II criteria (2004)*

1. Frontal headache, with pain in one of the following: face, ears or teeth
2. Clinical, endoscopic, or imaging (CT, MRI) evidence of acute, or acute-on-chronic, rhinosinusitis
3. Simultaneous onset of headache and facial pain with acute rhinosinusitis
4. Headache and facial pain resolve within 7 days of successful Rx of acute sinusitis

(Punch line: patient must have pus)

Chronic sinusitis is not validated as a cause of headache or facial pain

**Migraine is frequently mistaken for “sinus” headache!**

Because migraine:

- causes a pressure or tender feeling over the sinuses
- is frequently frontal or periorbital in location
- autonomic changes cause congestion (but clear)
- often responds to “sinus medication”
Tension-type Headache
ICHID-II Criteria (2004)

- Headache frequency varies
- Headache duration 30 min – 7 days
- At least 2 of the following
  - Location: bilateral
  - Quality: pressing/tight (non-pulsating)
  - Severity: mild or moderate
  - Activity: does not affect the pain
  - No more than one of: photophobia or phonophobia
  - No GI symptoms: e.g., nausea or vomiting, except anorexia
- Not attributed to another disorder

Migraine is frequently mistaken for tension-type headache

- Tension-type headache is more common
- Absence of “classical” features, e.g.
  - Aura
  - Vomiting
- Migraine and “tension headaches”
  - May not be distinct entities
  - Rather, they are two ends of a spectrum

Migraine

- What is migraine?
- How do you distinguish migraine from other headaches?

Migraine is a complex, (generally) stereotypical disorder of the nervous system typically characterized by:

- Recurrent, usually throbbing, unilateral headache
- About 20% of patients have an aura
- Associated fatigue, photopia, phonophobia, osmophobia, nausea, vomiting
- Other autonomic features (e.g., nasal congestion, syncope)
- Somnolence
- Cognitive dysfunction
- Migraine runs in families, but the genetics are not clear

Migraine Symptoms

- Prevalence of Migraine . . . 20%
  - Migraine with aura (classic) . . . 20%
  - Migraine without aura (common) . . . 80%
Spectrum of Migraine

- Prodrome: 3-72 hours in 40-60% of patients
- Aura: 5-30 minutes in 20% of patients
- Headache: 4-72 hours in ~96% of patients
- Recovery: variable
- Postdrome: variable

Migraine Prodrome

- Tired and weary*
- Difficulty concentrating*
- Stiff neck*
- Polyuria
- Hyperactive
- Lots of energy
- Yawning
- Pale face
- Photosensitive
- Phonosensitive
- Difficult thinking

*Most common

Giffin et al. Neurology 2003; 60:935

The Aura (warning)

Reversible focal neurological dysfunction
- Most commonly visual (90%)
- Can be sensory or motor
- Can affect language
- May cause vertigo
- May occur without headache
- Higher incidence of PFOs (?)

Fortification Spectra (Teichopsia)

The Alice-in-Wonderland Syndrome

Mixed Aura
Aura

- Typical aura: 5-30 minutes (average 20 min)
- Prolonged aura: > 60 minutes but < 7 days
- If greater than 7 days stroke
- Sustained aura (persistent positive phenomena) rare
  - ants, dots, flickering lights, heat waves, rain, snow, TV static

The American Migraine Study (AMS-2, 1999)

- USA - 28 million suffer from migraine
  - 51% either undiagnosed or misdiagnosed as sinus or tension headache
- 48% have a disabling migraine in a 3 month period
- A typical Migraine attack lasts 15 - 20 hours
  - Worldwide, about 240 million have migraine
- Epilepsy affects 2 million in the USA (Hauser et al 1991)

Diagnosing Migraine

By EXCLUSION

Migraine without aura (ICHD-II Criteria)

- Recurrent Headache (>5 attacks lasting 4 - 72 hours, not attributed to any other disorder, and with:
  - At least two of:
    - unilateral
    - pulsating
    - intensity
    - moderate - inhibits activity
    - severe - prohibits activity
    - worse with activity
  - At least one of:
    - Nausea or vomiting (or both)
    - photophobia or phonophobia (or both)
Chronic Daily Headache

Definition:

- Headache occurring for:
  - More than 15 days per month
  - For more than three months
- Prevalence 3-5%

Primary

- Short (< 4 hours)
- Long (> 4 hours)
  - With autonomic Sx
  - Without autonomic Sx

Secondary

- Obvious (common)
- Less obvious

Long duration: > 4 hours (without treatment)

- Transformed migraine
- CTTH
- Hemicrania continua
- New daily persistent headache (NDPH)

Short duration: < 4 hours (without treatment)

- Cluster headache
- Paroxysmal hemicrania
- SUNCT
- Ice pick-like headache
- Trigeminal neuralgia
- Hypnic headache

Prevalence of medication overuse headache

- 1.4% population overall
- 2.6% women
- 5.0% women over 50 years of age

Secondary Daily Headache

- Medication overuse (MOH), medication abuse (MAH)
- IH or s papilledema
- Low CSF pressure headache (SIH, CSF leak)
- Hemicrania continua, with a structural lesion
- Nummular headache, with a lesion
- Anemia
- Dystonia of the head or neck
- Giant cell arteritis
- Obstructive sleep apnea
- Dysthyroidism
- Sphenoid or ethmoid sinus disease
- Chronic meningitis (extremely rare)
- Somatization?

Structural Lesions and CDH

- Structural lesion
  - Chiari
  - Cerebral vein thrombosis
  - Mass
  - Cervical DJD (atlanto-axial subluxation)
  - Bilateral SDH
  - TMJ

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Department of Neurology
Cluster Headache

ICHD-II Criteria: At Least 5 Attacks With:

• Severe unilateral orbital, supraorbital and or temporal pain lasting 15-120 minutes untreated
• Attack associated with at least one of
  – Ipsilateral conjunctival injection and/or lacrimation
  – Ipsilateral nasal congestion and/or rhinorrhea
  – Ipsilateral forehead and facial sweating
  – Ipsilateral miosis and/or ptosis
  – Ipsilateral eyelid edema
  – A sense of restlessness or agitation*
• Frequency of attacks: 1 qod - 8 per day
• Not attributed to another disorder

Part II

The Pathophysiology of Migraine
Is Not fully understood

Pathophysiology

• Harold Wolf’s ‘vascular’ theory of migraine that:
  – Vasospasm of cerebral vessels -> aura
  – Followed by vasodilation -> throbbing pain
• Is superceded by the neurogenic theory

Clues to the Pathophysiology

• Prodrome: Hypothalamic/brainstem dysfunction
• Aura: Cortical dysfunction (CSD triggers vascular inflammation by releasing vaso-active peptides)
• Headache: Dysfunction in the trigeminocervical complex and trigeminovascular reflex
• Genetics: In Familial Hemiplegic Migraine (FHM)
  Autosomal Dominant mutations in:
  – P/Q Calcium channels (alpha 1 subunit)
  – Na+/K+ pump
  – Voltage Gated Sodium Channels

Summary Hypothesis

• A trigger activates the central generator
  – In migraine (dorsal raphe nucleus and locus ceruleus, or the cerebral cortex)
  – In cluster headache (posterior hypothalamus)
• In migraine - cortical spreading depression
  – alters cerebral blood vessel tone
  – initiates a trigeminovascular reflex to counter balance cerebral vasoconstriction by releasing mainly CGRP & VIP
  – Activation of the Trigeminal Nucleus Caudalis
  – Activation of the Superior Salivary Nucleus
  – Activation of the parasympathetic (vasoactive amine release)

Edvinsson & Uddman Brain Research Reviews 2005;48:438

Part III

Treatment
Migraine Management

1. Non-pharmacologic therapy
2. Abortive therapy
3. Prophylactic therapy
   a) Short term (during prodrome, aura, menses)
   b) Long term

- Explanation and reassurance
  - Naive patients need to hear “you don’t have a brain tumor”
- Identify and avoid triggers
- Behavioral modification
  - Regular diet, exercise, sleep hygiene, smoking cessation
- Stress management
  - Biofeedback
  - Relaxation therapy

Pharmacological Therapy

Most Medications We Use are **Off Label**

Abortive therapy

- Avoid narcotics
  - Bad medicine
  - Reinforces behavior
  - Causes withdrawal (rebound) headaches
  - Increased frequency + severity of subsequent HAs
  - Demerol is a relatively poor analgesic
    - Adversely affects ICP
    - Has epileptogenic metabolites
    - Causes dependency
    - Chronic opiate use stimulates facilitatory pain pathways

Abortive Therapy for Migraine

- First line (for mild headaches (OTC))
  - ASA
  - Acetaminophen
  - Antihistamines
  - NSAIDS: ibuprofen, naproxen

- Second line (for moderate headaches)
  - Combinations: Excedrin Migraine, Midrin, Fiorinal/Fioricet
  - NSAIDS: aleve 1100 mg, ketorolac, etc.
  - Dopamine antagonists (+- analgesic)
  - 5HT3 receptor antagonists
  - COX-2 inhibitor
    - Caution or avoid
Abortive Therapy for Migraine

- Third line (for severe/disabling headaches)
  - Dopamine antagonists (like thorazine)
  - 5HT₃ receptor antagonists
  - Ergot preparations, DHE-45, Migrale NS
  - Triptans (5HT₁₈/₁₉/₁₃ agonists)
  - COX-2 inhibitors

Status Migrainosus (HA >72 hours)
(or a prolonged migraine)

- Rehydrate (IV fluids)
- IV Dopamine antagonists
  - IV Compazine, Reglan
  - IM Phenergan
- DHE-45 (IV, IM)
- IV Depacon
- Ketorolac 60 mg IM
- Droperidol 2.5 mg IV x 3 (check Q-T interval)
- Corticosteroids
- Benadryl

The Triptans

- Almotriptan (Axert) . . Ortho-McNeil
- Eletriptan (Relpax) . . Pfizer
- Frovatriptan (Frova) . Elan
- Naratriptan (Amerge) . Glaxo
- Rizatriptan (Maxalt) . Merck
- Sumatriptan (Imitrex) . Glaxo
- Zolmitriptan (Zomig) . Astra Zeneca

Actions of the Triptans

- 5HT₁b cause vasoconstriction
  - Cranial (meningeal) arteries
  - Coronary arteries (less receptors than on cerebral vessels)
- 5HT₁d and 1f inhibit the trigeminal nerve
  - Peripherally: prejunctional at the neurovascular synapse
  - Centrally: in the trigeminal ganglion
  - Inhibition of 2nd order trigeminocervical neurons

Actions of the Triptans

Goadsby et al NEJM 2002; 346 (4):257-270

Site of Action of the Triptans
The Triptans

General contraindications
- Ischemic heart disease
- Uncontrolled hypertension
- Hemiplegic or basilar-type migraine (controversial)
- Known hypersensitivity
- Within 24 hours of other triptan or ergot alkaloid
- “Pregnancy”

Migraine Prophylaxis

- Explanation and reassurance
- Effective abortive treatment
  - Fear of further bad attacks removed
- Stress management
- Prophylactic medication
  - Short term (e.g. for “menstrual migraine”)
  - Long term (3 – 12 months)

Migraine Prophylaxis

Short Term

- Menstrual migraine
- Prodrome
  - NSAIDS
  - DA antagonists (especially during the prodrome)
  - Long acting triptans
- Aura
- Allodynia
  - Triptans work only if used early

Migraine

Indications for long term prophylaxis
- Previously, two or more episodes per month
- Significant interference with life*
  - occupation
  - social life
  - marriage
  - family
- Choice influenced by co-morbid conditions

Co-morbid Conditions

Psychiatric disorders are high in chronic daily headache patients

- Depression (bipolar)
- Anxiety
- Panic disorders
- Sleep disorders
  - Particularly insomnia
- Mitral valve prolapse
- Palpitations
- Obesity
- Irritable Bowel Syndrome
- Hypertension
- Ischemic Heart Disease
- Labyrinthine disorders
- Seizures
- Syncope

Migraine prophylaxis

Long term

Medications FDA approved for migraine
- Divalproex sodium (500-1500 mg daily)
- Propranolol (80-240 mg daily)
- Timolol (20-30 mg daily)
- Topiramate (100 – 200 mg nightly)
Migraine prophylaxis

- Tricyclics (amitriptyline)
- Beta blockers (atenolol, metoprolol)
- Calcium channel blockers (verapamil, diltiazem)
- 5HT antagonists (cyproheptadine)
- Other AEDs*
- ASA or NSAIDS
- Alpha blockers (clonidine, tizanidine)
- Anti-leukotrienes (Singulair, Accuprel)
- Other (MAO inhibitors, lithium)

Migraine

Less conventional management

- Neural blockade
  - Greater occipital nerve
  - Supraorbital nerve, supratrochlear
  - Cervical nerves
- Botulinum toxin
- Lidoderm patch
- Magnetic field therapy
- Alternative medicine

Alternative medicine

- Acupuncture
- Medications
  - Vitamin B-2 (riboflavin) 400 mg/d
  - Chelated magnesium diglycinate 600 mg/d
  - Feverfew 1 x tid
  - Coenzyme Q10 150 mg/day
  - Melatonin (cluster)
  - Butterbur

Patient

A 28 year old, woman complained of:

- Recurrent stereotypical headaches for the last 4-5 years
- Sometimes the “noises seem louder than usual” before the headache strikes
- There is photophobia and osmophobia
- The headache and the nausea interfere with her work and home life for up to 3 days
- Sometimes, the headache seem to be precipitated by lack of sleep or menstruation
- Her mother and sister suffer from “sinus headaches”
- General and neurological examination are normal

- What headache syndrome do you suspect?
- How would you manage her

Migraine without Aura

She had a prodrome, not an aura
What are the ICHD Criteria for Migraine Without Aura?

Migraine without aura (ICHD-II Criteria 2004)
Recurrence Headache (>5 attacks) lasting 4-72 hours, not attributed to any other disorder, and with:

- At least two of:
  - unilateral
  - pulsating
  - intensity
    - moderate - inhibits activity
    - severe - prohibits activity
    - worse with activity
- At least one of:
  - Nausea or vomiting (or both)
  - photophobia or phonophobia (or both)

Questions? Comments?

Dihydroergotamine Mesylate (DHE-45)
- Migranal (DHE nasal spray 4mgs)
  - 2 mg IN, repeat in 15 min
  - A 2nd amp. may be taken after 2 hours
  - Max 8 mgs/day (2 ampoules)
  - 4 amps/box
- DHE injection (1 mg)
  - 1 mg Sc/IM
  - may repeat after 1 hour
  - Max 2 mg/day or 4 mg/week
  - 10 amps/box

DHE-45
- General contraindications
  - Ischemic heart disease
  - Uncontrolled hypertension
  - Hemiplegic or Basilar-type migraine (controversial)
  - Known hypersensitivity
  - Within 24 hours of another triptan or ergot alkaloid
  - Caution with Raynaud’s phenomenon
Dihydroergotamine Mesylate
(DHE-45)

Time to maximal plasma level (Tmax)

- **IV:** 1-2 minutes (100% bioavailable)
- **IM:** 30 minutes (100% bioavailable)
- **Sc:** 45 minutes* (100% bioavailable)
- **IN:** 60-120 minutes (40% bioavailable)