Diagnosis and Management of Headache

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Walter is about to experience a nice visit from the migraine fairy.
Part I

Classification and Diagnosis
Headaches

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

Secondary
- SAH
- Infection
  - CNS or systemic
  - Sinus (15%)
- Abnormal ICP
  - Too high
  - Too low*
- Intracranial tumors
- Giant Cell Arteritis
- Trauma
Primary Headaches

Prevalence

- Tension headache . . . . 78%
- Migraine . . . . . . 12%
- Trigeminal Autonomic Cephalgias . 0.07%
  (Cluster Headache, M:F=6:1))
- Familial Hemiplegic Migraine . . 0.0002%
- Chronic daily headache . . . 3-5%
  (accounts for 70-80% office visits)
Secondary Headache
Sudden onset headache with loss of vision
Systemic causes of headache

- Giant Cell Arteritis
- Infections (encephalitis, meningitis, sinusitis)
- Increased PCO$_2$ (COPD, sleep apnoea)
- Mastocytosis
- Pheochromocytoma
- Severe rise in BP
  - >25% of diastolic, or
  - combined systolic and diastolic (~ 180/130)
- Toxins, drugs, and medications
Red Flags for 2\textsuperscript{0} Headache

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

- Atypical history
- New onset, or change in pattern
- Abnormal findings
  - fever, stiff neck
  - weight loss, jaw claudication, scalp tenderness, severe BP neurological deficit beware the numb chin or cheek
- Pre-existing risk factors
  - Immunosuppression, HIV
  - Hx of cancer
- Poor response to Rx*
Yellow Flags for 2° 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 3,582 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
What Now?
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
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

ICHDI-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
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)
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 it is clear)*
- *often responds to “sinus medication”*
Sinus congestion during migraine

Nasal Endoscopy During “Sinus” Headache

No Headache

With a moderate to severe “sinus” headache

1 hour after treatment with sumatriptan 6mg SC
Tension-Type headache
ICHD-II Criteria

• 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 except anorexia
e.g. nausea or vomiting
• Not attributed to another disorder
Migraine is frequently mistaken for Tension-type Headache

• Absence of “classical” features, e.g.
  – Aura
  – Vomiting

• Absence of a FH
  – Ask about ‘sick’ or disabling headaches
  – Ask about headaches in their children

• 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 it from other headaches?
Migraine

• In Europe the pronunciation is *(mee-graine)*, similar to the earlier French word *megrim*

• It comes from the Greek *hemikrania*
  – *Hemi* = *half*
  – *Kranion* = *skull*
Migraine is a complex 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
- Vertigo
- Migraine runs in families, but the genetics are not clear
Prevalence of Migraine

- General Population . 12%
  - Women . . . . 18%
  - Men . . . . 6%
  - Migraine with aura (classic) 20%
  - Migraine without aura (common) 80%
Age and gender specific prevalence of migraine

Rothrock et al. Neurology 1993
Migraine

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

Tired and weary*  blurred vision
difficulty concentrating* sensitive skin
stiff neck* constipation
polyuria dizzy
hyperactive nausea/vomiting
lots of energy hunger/craving
yawning thirst
pale face irritability
photosensitive emotional
phonosensitive difficulty reading/writing
difficulty thinking

* Most common

Giffin et al. Neurology 2003; 60:935
Figure 1. Migraine-associated symptoms.
Aura \textit{(warning)}

A reversible focal neurological deficit

- Most commonly visual (90%)
- Can be sensory or motor
- Can affect language
- May cause vertigo
- May occur without headache
- Higher incidence of PFO’s (?)
Fortification Spectra (Teichopsis)
Fortification Spectra
Fortification Spectra
Scintillating Scotoma

...selves through the usual round of work and play, a degree ness and a desire for rest are characteristic of severe migraines. A vascular headache, so exquisitely sensitive to every head move, in itself enforcing activity, but we do not only, or even the chief, mechanism at work. Many symptoms during an attack exhibit diminished tone of the skeletal muscles. Drowsy.

The relation of sleep to migraines, complex and further, and we will have to touch upon it in many contexts: the insomnias, stupor and stupor in the acute migraine (migraine and classical migraine), the tendency of migraines of this type to occur during sleep, and their relation to the so-called "migraine states." At this point we attention to the relationship: the of intense droop and the common the occasional attacks. The sleep of unusual and the typical protracted stupor in which many attacks have natural termination.

Nowhere in the literature can we find more vivid and descriptions of migrainous stupor than in Living's monogr...
Mixed Aura
The Alice-in-Wonderland Syndrome
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
Classification of Migraine

- Migraine with aura
  - Prodrome: 25%
- Migraine without aura
- Acephalgic Migraine
  - ~5%

Adapted from Lance
Diagnosing Migraine

BY EXCLUSION
Migraine without aura

(ICHDI-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 function
    • severe - prohibits function
  – Worse with routine activity

• At least one of:
  – Nausea or vomiting (or both)
  – photophobia or phonophobia (or both)
Screening Questions

1. Nausea?
2. Photophobia?
3. Disability?

• 2/3 + had a predictive value of 93.3% for migraine by the IDHD criteria
• 3/3 + had a predictive value of ~97% for migraine by the ICHD criteria

Lipton et al Headache 2003
Chronic Daily Headache
Chronic Daily Headache

Definition:

- Headache occurring for:
  - On more than 15 days per month
  - For more than three months

- Prevalence 3-5 %

Dodick NEJM 2006;354:158
Secondary Daily Headache

- MOH, MAH
- IIH c 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?
Sphenoid Sinus Disease
Chronic Daily Headache

Prevalence of medication overuse headache

- 1.4% population overall
- 2.6% women
- 5.0% women over 50 years of age
Risk Factors for CDH

- More than six headaches per month
- Obesity
- Low education
- Stress
- Head injury
- Snoring
- Medication overuse, or abuse
Cluster Headache
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
Trigeminal-Autonomic Cephalgias

- Cluster headache
  - Episodic
  - Chronic
- Paroxysmal Hemicrania
  - Episodic
  - Chronic
- Short Unilateral Neuralgiform headache with Conjunctival injection and Tearing (SUNCT syndrome)
Paroxysmal Hemicrania

- At least 20 attacks
- Attacks last 2-30 minutes
- At least 5 attacks per day
- Attacks completely prevented by therapeutic doses of: Indomethicin 25-75 mg tid (1/2 life 4 Hrs)
Part II

The Pathophysiology of Migraine is not fully understood
Pathophysiology

• Harold Wolf’s ‘vascular’ theory of migraine:
  – 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
Lashley's Aura

Karl Lashley, 1941
Cortical Spreading Depression

- CSD moves across the cortex at 3-6 mm/min. (average 3mm); similar to the cortical spreading depression of Leao (1944)
- The wave of CSD is associated with a biphasic or triphasic change in blood flow.
- A wave of reduced CBF is preceded by a hyperemia phase.
- It usually begins anterior to the occipital pole.
- The reduced CBF is not due to vasoconstriction
  - autoregulation is preserved
  - the vessels don’t respond to hypercapnia
Migraine Without Aura

Woods et al. NEJM 1994; 331(25):1689-1692
The Trigeminocervical complex and descending pain modulation pathways

The Trigeminovascular Reflex

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

- The release of vasoactive peptides causes
  - plasma protein extravasation (PPE)
  - mast cell degranulation
  - platelet adherence and aggregation
  - endothelial activation
  - formation of endothelial vesicles, vacuoles and microvilli

- Results sterile inflammation of the dural
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 (NO)
  – 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
Therapeutic Perspectives

- Headache Specialist
- Psychiatrist
- Neurologist
- ENT
- Pain Specialist
- Rheumatologist
Migraine Management

- Non pharmacologic therapy
- Abortive therapy
- Prophylactic therapy
  - Short term
    - Aura
    - Menses
    - prodrome
  - Long term
Non pharmacologic therapy
Non Pharmacologic Therapy

- **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 Medication We Use are Off Label
Migraine

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 the facilitatory pain pathways

Abortive Therapy for Migraine

• First line for mild headaches (OTC)
  – ASA
  – Acetaminophen
  – Antihistamines
  – NSAIDS: ibuprofen, naproxen, etc
Abortive Therapy for Migraine

• 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 (severe/disabling headaches)
  - Ergot preparations, DHE-45, Migranal NS
  - Triptans (5HT_{1b/d/f} agonists)
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
- Ketoralac 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

• $5\text{HT}_1\text{b}$ cause vasoconstriction
  – Cranial (meningeal) arteries
  – Coronary arteries (less receptors than on cerebral vessels)

• $5\text{HT}_1\text{d}$ and $1\text{f}$ inhibit the trigeminal nerve
  – Peripherally: prejunctional at the neurovascular synapse
  – Centrally: in the trigeminal ganglion
  – Inhibition of 2$^0$ order neurons in the trigeminocervical complex
Actions of the Triptans

Goadsby et al NEJM 2002; 346 (4):257-270
Site of Action of the Triptans
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”
Dihydroergotamine Mesylate (DHE-45)

Time to maximal plasma level ($T_{\text{max}}$)

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

• More than 2 headaches per month that significantly interfere with life (disability 3 or more days per month)
• Recurring headaches that significantly interfere with daily activity (occupation, social life, marriage, Family)
• Acute medication overuse (>twice a week)
• Acute meds C/I, ineffective or not tolerated
• Presence of uncommon variants
  – Hemiplegic migraine
  – Attacks with risk of permanent neurological damage
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)
• Methysergide (withdrawn in US)
Migraine prophylaxis

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

- **Lamotrigene:**
  - Rash in 4%
  - Rash in 14% (PH of AED induced rash)

- **Levetiracetam**
  - Behavioral side effects 16%
  - Worse if PH (especially treated depression)

- **Topiramate**
  - Cognitive 21.3%
  - Paresthesias (KCl), dysgeusia
  - Renal stones (hydration, HCTZ)
  - Narrow angle glaucoma

(JAMA 2004;291:615)
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
Possible Mechanisms of Action

- Amitriptyline
  - *Na channel blockade*
  - *Adenosine-mediated inhibition of descending nociceptive facilitation*
  - *Aminergic-mediated modulation of descending nociceptive facilitation*

- Gabapentin
  - *Modulation of intracellular calcium influx by binding to the $\alpha_2\delta$ subunit of calcium channels*

- Magnesium
  - *Blockade of NMDA receptors*

- Propranolol
  - *Aminergic-mediated modulation of descending nociceptive facilitation*

- Topiramate
  - *Potentiation of GABA inhibition*
  - *Antagonism of non-NMDA glutamate excitatory receptors*

- Valproate
  - *GABA-mediated inhibition of cell excitation*

- Verapamil
  - *Blockade of intracellular Ca and cell depolarization*

*Welch Neurology 2003; 61:S2-S8*
Migraine Symptoms
AMS-2

- Pulsatile
- Photophobia
- One-sided Pain
- Nausea
- Aura
- Vomiting
The Brainstem