8:10 AM **Vascular Causes of Headache**
Todd Schwedt, MD

8:50 AM **Pearls of Neuro-Ophthalmology**
Deborah Friedman, MD

9:30 AM **Migraine and Vertigo**
Jan Brandes, MD

11:00 AM **Cluster Headache**
Rebecca Wells, MD

11:40 AM **The Year in Review: Highlights of Headache Research 2012**
Morris Maizels, MD
Vascular Causes of Headache

Todd J. Schwedt, MD MSCI
Associate Professor of Neurology
Consultant
Mayo Clinic
Phoenix, Arizona

Objectives
• Describe the anatomic and physiologic relationship between the cerebrovasculature and pain
• Discuss thunderclap headaches
• Discuss some of the more common vascular causes of headache
  – Reversible Cerebral Vasoconstriction Syndromes
  – Intracranial Aneurysms
• Recognize other vascular causes of headache
  – Cervical Artery Dissection
  – Cerebral Venous Sinus Thrombosis
  – Others

Cerebrovasculature and Pain: Trigeminovascular System

Trigeminovascular System
• Nociceptive stimuli at any point along trigeminovascular system (including vasculature) can cause pain in the head and neck.
  • Cats - stimulate cranial vasculature - thalamic neuron excitation
  • Cats – stimulate superior sagittal sinus - increased metabolic activity and blood flow in trigeminal nucleus caudalis, cervical dorsal horn, dorsolateral spinal cord at C2, and VPM thalamus.
  • Humans - Focal headaches during balloon inflation in the ICA, MCA, vertebral artery, basilar artery (embolization procedures for AVM)

Disclosures
• Research Funding
  – National Institutes of Health
    – K23NS070891
  – National Headache Foundation
  – American Headache Society
  – Allergan
  – GSK
  – AGA Medical
  – Merck
  – ATI

• Consulting/Speaking
  – Allergan
  – Merck
  – Pfizer
  – Zogenix
Innervation of the Cerebral Vasculature

- Not Always Localizing
  - Trigeminal axons distribute mostly to ipsilateral arteries
    - A few fibers cross to innervate contralateral arteries
  - Single trigeminal ganglia cells may innervate several arteries
  - Midline vessels may have bilateral sensory innervation

- Likelihood of pain relates to density of sensory innervation
  - Proximal > distal
  - Posterior circulation > anterior circulation
  - Manipulation of posterior vessels is twice as likely to cause pain

Thunderclap Headaches

Thunderclap Headache

- Severe, sudden, reaches max intensity in <1 minute.
  - Not just "the worst headache of your life"
  - Must become that severe quickly

- TCH is a medical/neurologic emergency

- Secondary TCH
  - Can be associated with significant morbidity/mortality

- Primary TCH
  - Diagnosis of exclusion
  - Comprehensive evaluation is required

General Diagnostic Approach to TCH

All Patients – Emergent Evaluation:
- Clinical History
  - Absence of accompanying symptoms cannot be relied upon for dx
- Physical and neurologic examination
- CT brain no contrast
- If CT is non-revealing and does not contraindicate, then LP

Consider:
- If diagnosis has not been reached, then MRI brain with gadolinium
- Angiography
  - MR, CT, or conventional

Thunderclap Headache Frequency of Secondary Causes?

- Prospective study (n=113) of TCH
- Secondary cause in 60 (53%)
  - RCVS - most common – 29 cases
    - 26% of TCH cases
    - 48% of secondary cases
  - SAH – 15 cases
    - 13% of TCH cases
    - 25% of secondary cases

More Common Vascular Headaches

- Reversible Cerebral Vasoconstriction Syndromes (RCVS)
- Intracranial Aneurysms
  - Subarachnoid Hemorrhage
  - Sentinel Headache
**Reversible Cerebral Vasoconstriction Syndromes (RCVS)**

1. Thunderclap headache with or without additional neurologic signs or symptoms
2. No evidence for aneurysmal subarachnoid hemorrhage
3. Multifocal segmental cerebral artery vasoconstriction
4. Normal or near-normal CSF (protein<80mg, wbc<10/mm³, normal glucose)
5. Angiographic reversibility <12 weeks after onset


**RCVS: Clinical Presentation**

- Women > Men (3:1)
- Peak Incidence: 20 – 50 years of age
- Recurrent TCHs (think RCVS)
  - Mean 0.7 headaches per day
  - Most 2-10 total headaches
  - Duration: median 14 days (6-86 days)
- Other Symptoms
  - Nausea/vomiting, photophobia, blurred vision
  - Seizures, focal neurologic deficits


**RCVS: Etiologies/Provoking Factors**

- Drugs
  - Illicit drugs: cannabis, cocaine, ecstasy, amphetamines, LSD
  - Serotonergics: SSRIs, triptans
  - Sympathomimetics: ephedrine, diet pills
  - Immunosuppressants
  - Ergots
  - Binge alcohol
- Pregnancy and Post-partum

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exertion</td>
<td>38</td>
<td>77</td>
</tr>
<tr>
<td>Defecation</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>Spitting</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Anger/hot flashes</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Googling</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>Sexual activity</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Shaving/shaving</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Irritation with effort</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Bending/bending</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Page</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>


**Multifocal arterial narrowing or “beading”**
RCVS: Complications

- Cortical Subarachnoid Hemorrhage up to 1/3
- TIA 15%
- Cerebral Edema (PRES) 10-15%
- Intracerebral Hemorrhage up to 10%
- Ischemic Stroke 5%
- Subdural Hematoma 2%

<table>
<thead>
<tr>
<th>Delay from HA onset to</th>
<th>Mean # days [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of Cerebral Hematoma</td>
<td>1.7 [0-4]</td>
</tr>
<tr>
<td>First Seizure</td>
<td>3 [2-4]</td>
</tr>
<tr>
<td>Diagnosis of PRES</td>
<td>4 [1-6]</td>
</tr>
<tr>
<td>Diagnosis of SAH</td>
<td>5 [0-20]</td>
</tr>
<tr>
<td>Last TCH</td>
<td>7.4 [0-28]</td>
</tr>
<tr>
<td>Transient Neurologic Deficits</td>
<td>11.6 [0-23]</td>
</tr>
<tr>
<td>Diagnosis of Ischemic Infarct</td>
<td>12 [9-15]</td>
</tr>
</tbody>
</table>


RCVS: Complications – Convexity SAH

CT scan - superficial convexal SAH along bilateral posterior frontal lobes (arrow).

Angiogram - RCVS

RCVS: Complications – ICH

- Mostly, cSAH, followed by ICH, SDH
- Risk factors
  - female (OR, 4.05)
  - migraine (OR, 2.34)

CT – Multiple ICH in patient with RCVS

Ducros A et al. Stroke 2010;41:2505-2511

RCVS: Complications – PRES

1) Bilateral parieto-occipital vasogenic edema (arrow).
2) Hyperintense dots (arrowheads) in sulcal spaces – dilated cortical surface arteries

MRI – FLAIR:
- Bilateral parieto-occipital vasogenic edema (arrows)
- Hyperintense dots (arrowheads) in sulcal spaces – dilated cortical surface arteries

CTA

Transfemoral angiogram CTA – 3 months later

Chaterjee M et al. Neurology 2010;75:1939-1941

RCVS: Treatment

- No randomized controlled trials; Unknown whether influences outcome
- CaCCBs may prevent recurrent TCH
- Nimodipine [30-60mg every 4-8h; 0.5-2 mg/h IV]
- Verapamil [40-120mg every 8h]

RCVS: Outcomes

- Mean duration complete angiographic resolution 63d (13-157d)
- Long-term disability due to stroke and other complications (<10%)
- Symptom recurrence is rare
RCVS vs. Primary Angiitis of the Central Nervous System

<table>
<thead>
<tr>
<th></th>
<th>RCVS</th>
<th>PACNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute (seo-min)</td>
<td>Subacute - chronic</td>
</tr>
<tr>
<td>Headache</td>
<td>Acute, severe often thunderslap</td>
<td>Insidious, progressive</td>
</tr>
<tr>
<td>CSF</td>
<td>Normal, near normal</td>
<td>Abnormal in &gt;90%</td>
</tr>
<tr>
<td>CT/MRI</td>
<td>Normal, PRES, watershed stroke</td>
<td>Abnormal in &gt;90% WmH and cortical/subcortical infarctions</td>
</tr>
<tr>
<td>Angio</td>
<td>Diffuse, segmental stenosis; large central arteries; reversible</td>
<td>Cutoff, irregularity, smaller vesse; often irreversible</td>
</tr>
</tbody>
</table>

WMH=White matter hyperintensities

*Calabrese L, Dodick DW, Schwedt TJ, Singhal A. Ann Int Med 2007.*

### Aneurysm and Headache

**Subarachnoid Hemorrhage**

- 10 to 25% of patients with TCH
- Diagnosis of first consideration
  - Significant morbidity and mortality
    - 10% die before reaching hospital
    - 50% overall fatality rate
    - 1/3 of survivors remain dependent

- Headache
  - Most common presenting symptom – typically TCH
    - Isolated symptom in up to 70% of those in outpatient setting
    - Isolated symptom in about 1/3 of patients overall
  - Loss/alteration of consciousness, seizures, stroke, visual change, nausea, vomiting, dizziness, neck stiffness, photophobia.

- CT brain no contrast
  - Regardless of timing: sensitivity = 93%
    - Sensitivity decreases with time
      - Near 100% within first 6 hours (95% CI 97-100%)
      - Day 2 = 86%
      - After 2 days = 76%
      - After day 5 = 58%
  - Assumptions
    - Modern CT scanner
    - Highly skilled reader

- Lumbar Puncture
  - Up to 3% of patients with TCH and negative CT have CSF evidence for SAH
  - More sensitive >12 hours after SAH
  - Opening pressure, routine studies including cell counts, visual inspection for xanthochromia, spectrophotometry (if available)
    - Spectrophotometry sensitivity is greater than 95% when CSF is collected at least 12 hours after SAH (up to 2 weeks)


**Subarachnoid Hemorrhage**

- If CT is non-revealing and if LP not contraindicated, then LP

Sentinel Headache

- Warning headache of SAH
  - Most common within 2 weeks preceding SAH
    - Peak incidence within 24 hours; minor peak 7-14 days prior
  - No meningismus, altered consciousness, local neuro signs/symptoms.
  - Occur in 10 to 43% of patients prior to SAH
  - ?caused by minor blood seepage into SAH or changes in aneurysm wall
  - Treatment of underlying aneurysm avoids mortality/morbidity of SAH.

- Only diagnosed in retrospect
- Intracranial aneurysms in 3.2% of gen pop
- Thus, relationship uncertain

Unruptured Aneurysms and Headache (without TCH)

- ?associated with headache even if no SAH and no TCH
  - Patients think so
  - Some physicians think so
  - Presenting symptom in at least 1/3 of cases

Headaches After Treatment of Unruptured Aneurysms

Small Prospective study – headache frequency

- Pre: 31/90 days
- Post: 17/90
  (p<.001)

  - Reduced: 50%: 68% of patients
  - New/worsened: 9% of patients

  - Reasons for improvement: Unclear
  - Predictors of no improvement: Pre-Intervention migraine, severe headaches, anxiety, stent-assisted coiling

  - Results similar to 2 retrospective studies – majority improve

Cervical Artery Dissection

- Annual incidence: 2.6 per 100,000 population.

- Headache is the most frequent presenting symptom
  - Carotids: 60 to 95%
  - Vertebrais: 69%

- Mode of Onset
  - Most commonly gradual onset-pain
  - TCH in 20% of patients

Cervical Artery Dissection

- Location: almost always ipsilateral to dissected artery
  - Carotid: orbital, frontal, temporal, 1/3 with neck pain
  - Vertebral: occipital or parieto-occipital, 2/3 with neck pain

- Quality: Constant, steady aching

- Severity: Quite variable from mild to severe

- Duration
  - Carotid: vast majority (90%) resolve within 1 week
  - Vertebral: may last up to 5 weeks
Cervical Artery Dissection

- Unusual for patient to present only with head or neck pain without associated symptoms, but does occur.
- Median interval from onset of headache to other neurologic manifestations:
  - Carotid: 4 days
  - Vertebral: 14.5 hours
- Associated Clinical Manifestations
  - Amaurosis fugax
  - Stroke
  - Horner's syndrome
  - Pulsatile tinnitus
  - Dysgeusia
  - Diplopia
  - Amaurosis
  - Vertigo


Cerebral Venous Sinus Thrombosis

- Occlusion of 1 or more draining veins or sinuses
- Headache – most common symptom – 75%
  - Cause of new daily persistent headache
  - Worse - lying down, pressure increases (cough, sneeze, bending, Valsalva)
  - TCH in <10%
  - 25% with headache as isolated symptom
  - Focal deficits (e.g. hemiplegia, visual change, altered mental status, tinnitus)
  - Seizures
- Predisposing
  - Hypercoagulable
  - Pregnancy
  - Dehydration
  - Oral contraceptive use
  - Cancer
  - Head Trauma


Cerebral Venous Sinus Thrombosis

- Exam
  - Papilledema
  - Focal neurological deficits
- Brain CT
  - Low sensitivity and specificity – normal in 25%
  - Empty delta sign, dense vein sign, cord sign
  - Edema, hemorrhage (venous)
- LP
  - Normal in 70%
  - High opening pressure (only abnormality in many patients)
  - Lymphocytic pleocytosis, high RBC, and/or high protein in 30%


Cerebral Venous Sinus Thrombosis

- MRI – Edema, Hemorrhage
- Vascular imaging – MRV, CTV, Catheter Angiogram
- Thrombosis
  - Must differentiate from congenital asymmetry (very common)

Other Vascular Headaches
Other Vascular Headaches

- Ischemic Stroke
- Arteritis
- Post Angiography/Angioplasty
- Post Endarterectomy
- Vascular Malformations
- Intracranial Hemorrhage

Conclusions

- Numerous causes of vascular headaches
  - More common
    - Posterior circulation
  - Proximal portions of arteries

- Acute - TCH
  - Medical Emergency – systematic evaluation
  - At least ½ are secondary (probably higher)
    - RCVS – at least ½ of secondary cases; recurrent TCHs
    - SAH – 25% of secondary cases
    - ?unruptured aneurysm

- Subacute/Chronic
  - Cervical artery dissection
  - Cerebral venous sinus thrombosis
  - Others

Thank You!
Neuro-Ophthalmology Pearls for the Headache Specialist

Deborah I. Friedman, MD, MPH
University of Texas Southwestern Medical Center
Dallas, Texas

Topics
• Is it a Horner Syndrome?
  • Examination of the pupils
  • Case presentation and differential diagnosis
• Double vision
  • Evaluation of diplopia
  • Case presentation and differential diagnosis
• Papilledema?
  • Tips on ophthalmoscopy

Case 1.
45-year-old man at work in forensic psychiatric facility and felt a “pop” in his neck
Developed pain in right temple
Severe, steady, not throbbing
Photophobia, no photophobia, nausea, vomiting

In the E.D.
• Looks uncomfortable
• Right eyelid is a little droopy
• Is the right pupil smaller? Not sure
• Neurological exam otherwise normal

Possibilities (Big Picture)
• Headache and Horner syndrome
• Headache and 3rd nerve palsy
• Headache and ptosis

Possibilities

<table>
<thead>
<tr>
<th>Possibility</th>
<th>Pro/Con</th>
<th>Likely?</th>
<th>Serious?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache and Horner Syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid dissection</td>
<td>Could be</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid thrombosis</td>
<td>No other Sx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster headache</td>
<td>Duration, no Hx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>New, not all Sx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavernous sinus problem (apoplexy)</td>
<td>No diplopia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem stroke</td>
<td>Not in isolation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Horner Syndrome

Oculosympathetic palsy
Ptosis
Miosis
Dilator lag of pupil
Anhidrosis (if preganglionic)
Iris heterochromia (if congenital)

Examination of the Pupil - Tools

- Bright light source
- Near card with pupil gauge
- Light switch
- Curtain/mini-blind controls

No-Fail Pupil Examination

With patient looking straight ahead in the distance
1. Measure pupil size in the light
2. Measure pupil size in the dark (how?)
   Illuminate from below

Leave the room dark for steps 3 - 5:
3. Check reaction to light in each eye
   Does it react? How fast? How well?

Afferent Pupillary Defect

4. Swinging flashlight test
   Shine light directly into one eye
   Immediately swing light to other eye
   Hold for 1-2 seconds on each eye
   Should see initial constriction each time

APD: The direct response is not as good as the consensual response WAS.

What if one pupil is damaged and won’t react to light?

Check for APD using “reverse” technique
Look at the response of the normal pupil
The direct response is better than the consensual response.... there is a left APD

5. Check the near response if needed

Best seen in a dark room, illuminate from below
Check if poor reaction of either pupil to light
Age and “talent” limited
Must be able to cross eyes
Afferent information is provided directly to the brainstem, bypassing the optic nerves
Distinguishes afferent from efferent problem
Summary of Pupil Exam

1. Size in the light
2. Size in the dark
3. Reaction to light
4. Swinging flashlight test for APD
5. Response to near, if needed

Ptosis

1. Is ptosis present?
   Lid Fissure Height –
   Lid margin to lid margin

Note: "Upside down" ptosis may be present in Horner syndrome

Findings in Horner Syndrome

PUPILS
Anisocoria is greater in the dark (the normal pupil dilates in the dark, Horner’s pupil does not).
Normal light reaction in both eyes
Pharmacologic testing (not widely available)

LIDS
Affects Müller’s muscle...Levator is normal
Lid fissures:
  2-3 mm of ptosis (smaller fissure on affected side)
Levator function: Equal!

Sympathetic Pathway

Post-ganglionic
Pre-ganglionic
NE

Pre-ganglionic
ACh

Levator vs. Müller’s muscle?

1. Line up ruler with lid margin
2. Read where upper lid margin intersects the ruler

Look all the way down
Look all the way up

Back to the Patient

Acuity
20/20 OU

Pupils
Light 3 mm OD, 4 mm OS
Dark 3 mm OD, 5 mm OS
Normal reaction, no APD

Lid fissures
2 mm of right eye ptosis

Levator
17 mm OU

Fundi and neurologic exam normal
Case 2.

77-year-old woman with diplopia for one year
Saw optometrist, corrected with prisms
Diplopia returned 8 months later
Vertical, binocular, not improved with prism
One month later - right lid started drooping
Occasional ache in back of right eye, no real
headache, visual loss, other neurologic
symptoms

PMHx - pre-menopausal migraine, arthritis
Meds – Oxaprozin (Daypro), Premarin,
tolteradine (Detroil), glucosamine,
chondroitin, vitamin E, MVI
FHx - Father died of MI, daughter with HTN
ROS - nocturia

Diplopia - Taking the History

Three critical questions:
1. Monocular or binocular?
2. Vertical or horizontal?
3. Does it worsen in any position of
gaze?

Monocular or binocular?

Diplopia originating from one eye or when using
both eyes together?
What happens when EITHER eye is closed?
Monocular - almost always ocular (refractive)
Binocular - extraocular muscle or neurogenic
problem
Incomplete or true diplopia will improve with
monocular viewing

Vertical or Horizontal?

*Horizontal diplopia* - medial or lateral recti
Crossed images – exodeviation (out)
Uncrossed images – esodeviation (in)

Examples:
Sixth nerve palsy
Internuclear ophthalmoplegia (INO)
 Decompensated horizontal phoria

*Vertical diplopia* - malfunction of vertically
acting muscles (superior and inferior rectus,
superior and inferior obliques) or central
vestibular pathways
Rarely truly "vertical" - oblique or torsional
Examples:
Third and fourth nerve palsies
Skew deviation
Decompensated vertical phoria
Worse in any direction of gaze?

Area of largest separation = action of maximally paretic muscle
Examples:
- Fourth nerve palsy - worst down and inward
- Sixth nerve palsy - worst in direction of paretic muscle/nerve
- INO - worst with horizontal gaze to contralateral side (action of adductor)

Exam
Versions: Both eyes together
Ductions: One eye at a time (sometimes easier)
Up, down, horizontal (obliques – vertical or torsional)
What if it’s so subtle you can’t see it??

Dissimilar images
(red glass, Maddox rod)

It is all UPSIDE DOWN and BACKWARDS (think Ginger Rogers)

Dissimilar Image Tests
Maddox Rod Test
Series of parallel cylinders that convert a point source of light into a linear streak
Streak is oriented 90 degrees to parallel cylinders
Breaks fusion
Used to detect horizontal and vertical deviations

Rod placed over OD in direction desired
To measure vertical deviation – lines vertical
To measure horizontal deviation – lines horizontal
Patient fixates on point source of light
Patient will observe a red line (OD) and a white light (OS)

Red glass: sees red dot and white dot
The orientation reported by the patient corresponds to the relative locations where the images fall on the retina.
This is upside down and backwards from the position of the eyes.
Example: Red line/dot on left – right eye is on the right (exo deviation, eyes turned out)
Use prisms, finger width or cm/inches to quantify in different directions of gaze
Our Patient’s Exam

- Acuity 20/30 OU
- Optic nerve functions normal
- Pupils: Light 6 mm OD, 3 mm OS
  Dark 6 mm OD, 4 mm OS
  No reaction OD, no APD
- Lid fissures: 3 mm of right ptosis
- Levator: 6 mm OD, 12 mm OS

Motility
- OD: 50% supraduction, adduction
  10% infraduction
  NL. abduction, incyclotorsion*
- OS: Normal
- Tangent screen fields, fundi - normal
- Neurologic exam: Corneal reflex intact OU
- Vital signs: BP 166/93

Possibilities

<table>
<thead>
<tr>
<th>Headache and Third Nerve Palsy</th>
<th>Pro/Con</th>
<th>Likely?</th>
<th>Serious?</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. Comm Aneurysm</td>
<td>Fluctuation, duration</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td>Normal vision and fields, little HA</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>&quot;Ophthalmoplegic migraine&quot;</td>
<td>Duration, no significant pain</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>Pupil</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Microvascular III</td>
<td>Course, pupil</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Tumor</td>
<td>Could be</td>
<td>✅</td>
<td>✅</td>
</tr>
</tbody>
</table>

It Must be the Ophthalmoscope

- Make sure battery is charged
- Patient sits, you stand (ipsilateral to eye, just to side of knee)
- Switching eyes helps
- Dilating the pupils helps even more
- Hand/finger position (index finger on the dial)
- Put lens on zero (don’t worry about the numbers)
- GET REAL CLOSE, THEN GET CLOSER (middle finger on the cheek)
- Move your whole body to redirect gaze
- Focus by changing the dial (index finger)
- PRACTICE

Optic Disc

- Temporal margin should always be sharp
- Nasal margin may be indistinct
- Relatively flat (diopter change needed?)
- Venous pulsations: look at veins on the disc (patient must fixate well)
- Macula – swing about a disc diameter temporally (glare)
- When in doubt, consult ophthalmologist
Normal

That's the macula. It never looks this good in real life; your area of view is smaller

Temporal disc margin should be sharp

Abnormal

Take Home Points

- The near card is your friend
- Remember the "no fail" exam for pupils
- Measure lid fissures and levator function
- The diplopia exam can be confusing but don't be intimidated
- When in doubt:
  Deborah.Friedman@UTSouthwestern.edu
  NOVEL site www.novel.utah.edu
Migraine and Vertigo

• Vertigo that is causally related to migraine - migrainous vertigo
• Vertigo syndromes not caused by migraine but with statistical association possibly as a result of an association with both
• Vertigo that coexists with migraine in the same patient by chance

Migraine and Vertigo

• Vertigo that is causally related to migraine - migrainous vertigo
• Vertigo syndromes not caused by migraine but with statistical association possibly as a result of an association with both
• Vertigo that coexists with migraine in the same patient by chance

Migrainous Vertigo

• Vertigo- independent migraine symptom which usually does not correspond to aura
  – May dissociate from headaches
• Benign paroxysmal vertigo of childhood
• Benign recurrent vertigo
• Vertigo as a migraine equivalent
• Migraine-associated dizziness
• Migraine-related vestibulopathy
• Vestibular Migraine
Clinical Presentation of Migrainous Vertigo

- Spontaneous vertigo → Positional Vertigo
- Head motion intolerance
- Nausea and imbalance
- Duration of vertigo
  - Seconds to hours to days
- Vertigo with typical duration of aura:
  - 10-30% of patients

Diagnostically J Neurol 1999; 246:883

Migrainous Vertigo as Aura?

- Can precede, begin with, or appear late in headache phase
- May occur with and without headache
- Vertigo and headache may never occur together in some patients
- Associated symptoms may include photophobia, phonophobia, and visual or other auras
- Rare symptoms: transient hearing loss and tinnitus

Not wise to demand a temporal association between HA and vertigo

- 40 patients with recurrent vertigo
- Also had IHS migraine
- Second study group of 40 were taken from relatives of presenting patients
- Marked female preponderance
- Migraine onset in teens, vertigo years later
- 50% had aura

Brantberg, Tress, Babbs, BW. 22a03: AAI 125:3, 276-279.

Diagnosis of Definite Migrainous Vertigo

- Episodic vestibular symptoms of moderate severity
  (rotational, illusory self/object motion, positional vertigo, head motion intolerance)
- IHS migraine diagnosis
- During two vertigo attacks/ one of:
  - migraine headache
  - photophobia
  - phonophobia
  - aura

Diagnosis of Probable Migrainous Vertigo

- Episodic vestibular symptoms of moderate severity
  (rotational, illusory self/object motion, positional vertigo, head motion intolerance)
- One of following:
  - IHS migraine
  - Migraine symptoms during >2 attacks of vertigo
  - Common migraine triggers of vertigo in >50% of attacks
  - Migraine Rx effective for vertigo
- Other causes ruled out

Migrainous Vertigo and IHS Classification of Migraine

- Vertigo not included in IHS classification except in basilar type migraine
- Vertigo as a basilar migraine aura symptom lasts between 5-60 min and is always followed by headache
- A second aura symptom from posterior circulation is required (dysarthria, double vision, or bilateral paresthesias)

Sturzenegger and Meienberg Headache 1985;25:408
Clinical and Neurotologic Findings

- Unilateral hypoexcitability to caloric stimulation in 21%
- 10% have directional preponderance of nystagmus; 34% ENG abnormalities
- Mild central oculomotor deficits
- May be completely normal
- Neurotologic abnormalities - 0-83%
- Intercritical hearing loss rare

Disease Spectrum of Migraine Related Vertigo

- Migraine Related Vertigo
  - Probable Migrainous Vertigo
  - Definite Migrainous Vertigo
  - Basilar Type Migraine

Distribution of Severity

- Frequency did not differ between the three groups
- Sequential relationship between headache and vertigo showed: BtM 80% and dMV 67% showed sequential relationship between HA and vertigo, 84% of pMV had HA or vertigo independently
- Precipitants similar for all 3 groups
- Neurological symptoms highest in BtM
- BtM higher % of saccadic dysmetria 40% (10% with dMV and 16% of pMV)

Pathophysiology of Migrainous Vertigo

- Spreading depression
- Neurotransmitter modulation of vestibular neuron activity
  - Calcitonin-gene related peptide
  - Serotonin
  - Noradrenaline
  - Dopamine
- Familial hemiplegic migraine and episodic ataxia type 2
  - Vertigo and migraine as prominent symptoms

Subclinical Cerebellar Impairment in Common Types of Migraine

Excess Glutamate and K+ equals hyper-excitability and CSD propagation
Differential Diagnosis of Migrainous Vertigo

- Benign positional vertigo (BPV) – most common
- Psychiatric dizziness – second most common
- Meniere’s disease
- Central positional vertigo
- Vertebrobasilar TIA
- Vascular compression of the 8th nerve
- Perilymph fistula
- Autoimmune inner ear disease
- Schwannoma


Evaluation of Vertigo and Headache

- Establish headache diagnosis
- Elicit vestibular vs. non-vestibular
- Look for temporal association
- Ask about duration
- Find trigger factors
- Check fundi, EOM, hearing, Romberg, finger-nose, heel/toe/tandem, HTS, orthostatic BPs
- Consider MRI and neuro-otologic evaluation

_prophylactic treatment of “Migraine-Related Vertigo”_

Medication Optimal Dosing:
- Propranolol 40-160mg
- Metoprolol 100-200mg
- Clonazepam 0.25-1.0mg
- Flunarizine 5-10mg
- Amitriptyline 10mg

- 53 patients from 652 vertiginous patients
- 36% completers; only 3 reported benefit
- 69.3% had complete disappearance of spells
- 81.8% had >50% reduction in attacks


Treatment of Migrainous Vertigo: Acute

- Acute Treatment
  - Ergotamine
  - Sumatriptan
  - Vestibular suppressants
    - Promethazine
    - Meclizine
    - Prochlorperazine
    - Benzodiazepines
    - Single placebo-controlled trial with zolmitriptan
  - Inconclusive due to low power


Treatment of Migrainous Vertigo: Prophylaxis

- Evidence-based recommendations are lacking
- Medications for prophylaxis:
  - Propranolol
  - Metoprolol
  - Pizotifen
  - Flunarizine
  - Acetazolamide
  - Topiramate
  - Zonisamide
- Stepwise treatment:
  - Avoidance of food triggers
  - Low-dose tricyclic antidepressants and a beta-blocker

Migraine and Meniere’s Disease

- Association described by Prosper Meniere in 1861
- Prevalence of migraine in Meniere’s disease is more than twice as in the general population
- Postulated that an ear damaged by repeated migraine attacks (with resultant auditory and vestibular deficits) results in development of endolymphatic hydrops

Migraine and Motion Sickness

- Occurs more frequently in patients with migraine (30 to 50%)
- More pronounced in children and in migraine with aura
- Nausea and dizziness improving after cessation of motion suggest motion sickness
- Rotational or positional vertigo persisting after absence of motion suggests MV

Vertigo as a Symptom of Migrainous Infarction

- Migraine and increased stroke risk
- Migrainous infarction predominantly in posterior cerebral artery territory
- Vertigo as a sole neurologic symptom is rare as a transient ischemic attack presenting symptom

Migrainous Symptoms During Meniere Attacks

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Migrainous headache</th>
<th>Photophobia</th>
<th>Aura symptoms</th>
<th>At least one of the three</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td>25</td>
<td>61</td>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>Sometimes</td>
<td>23</td>
<td>9</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>Never</td>
<td>52</td>
<td>30</td>
<td>84</td>
<td>18</td>
</tr>
</tbody>
</table>

32 year woman with vertigo and chronic migraine

- Hx of episodic migraine with aura since 12
- Four spontaneous abortions
- D&C after last, 49 hours post op, developed crash migraine and severe vertigo
- Abnl ENG, “normal” MRI of brain
- Persistent vertigo and headache for next 16 mos
- Stacked risks: post partum, surgical, hypercoagulable

Migraine and Cerebellar Symptoms

- Familial hemiplegic migraineurs (FHM) may develop progressive cerebellar ataxia and nystagmus
- Mutations in the CACNA1A gene identified in FHM and also in episodic ataxia type 2 (EA-2) and spinocerebellar ataxia type 6
- EA-2 is characterized by short bouts of cerebellar ataxia, usually with vertigo and interictal nystagmus
- 50% of EA-2 patients have migraine

Shared Genetics

- Familial Hemiplegic Migraine chr m 19p; 1q
- Familial Benign Recurrent Vertigo chr m 22q
- Ion channel mutations shared by ear and brain could explain combination of central and vestibular signs and common triggers for migraine
- Ion channels in inner ear critical for maintaining potassium-rich endolymph and neuronal hyperexcitability, thus defects could lead to reversible hair cell depolarization>>auditory and vestibular symptoms

Migraine and Non-Vestibular Dizziness

- Dizzy spells are also more frequently reported by migraine patients than in controls
- Syncope reported in 5% of migraine attacks
- Orthostatic symptoms
- Psychiatric comorbidities
- Medications, often migraine prophylactics

Association between Migraine and Autonomic Nervous System Dysfunction

- Elevated prevalence of syncope and orthostatic intolerance in migraine during attacks but not interictally (CAMERA study)
- Disabling migraine attacks had elevated diastolic BP and lower pulse rates .....not seen in nondisabling attacks, suggesting ANS dysfunction may be a consequence of frequent disabling attacks

Vertigo in Midlife

- A 55 year physician presents with new onset shortness of breath, tachycardia and a “hint” of vertiginous sensations 10 days after total vaginal hysterectomy and bilateral oophorectomy
- Hx of migraine with aura; osteopenia
- On estrogen/progesterone patches qwk
- No other significant past medical hx

What to do?

- Diagnostic tests
- Examination
- Differential diagnosis

Tests/Studies?

- Chest xray negative
- Doppler lower extremities: normal
- Chest CT negative
- Hypercoagulable studies: normal
- Oxygen saturation: sitting – 98%
- Oxygen saturation: on walking 30 feet – 87%
- Tachycardia to 140-150

Course over 3 weeks

- Three hospital admissions
- Persistent vertigo, shortness of breath, and rapid heartbeat with any activity: showering, walking, dressing
- Working from a chair in office
- Vertiginous with all episodes; no visual aura
- No symptoms except intermittent tachycardia while supine

Any other questions or studies?

Answers?

- 24 hour Holter:
- Cardiac ECHO: normal
- Pulmonary consult: no answers
- Cardiology consult: tilt table testing
- Tilt table testing: loss of consciousness at 9 minutes, preceded by tachycardia, nausea, vertigo, SOB

Postural Orthostatic Tachycardia Syndrome (POTS)

- A condition of dysautonomia and orthostatic intolerance
- Hallmark symptom is an increase in heart rate from supine position to upright of more than 30 b/min
- Or to a heart rate greater than 120 b/min within 10 min of headup tilt

Tachycardic Response in POTS

- Lightheadedness, presyncope, dizziness, but NOT vertigo
- Exercise intolerance
- Extreme fatigue
- Syncope
Symptoms of POTS

- Chronic or acute hypoperfusion: depression
cold extremities
headache
disorientation
- Autonomic dysfunction: nausea/vomiting
diarrhea
abdominal pain
constipation
- Cerebral hypoperfusion: difficulty finding the right word
impaired concentration
visual
- Sleep disturbances

Etiology of POTS

- Not fully known
- Alpha-receptor and Beta-receptor hypersensitivity
- Hyperdopaminergic states
- Elevated plasma norepinephrine...hyperadrenergic state
- Reduced venous return
- Sympathetic overactivity

Conditions associated with POTS

- Vasovagal syncope
- Chronic fatigue
- Fibromyalgia
- Irritable bowel syndrome
- Ehler-Danlos Syndrome
- Restless Legs Syndrome
- Postoperative deconditioning

Diagnosis of POTS

- Onset
  - rapid growth in teens
  - post-viral
  - post-traumatic
  - genetic
  - pre or post pregnancy
  - 70-80% are menstruating females
  - de-conditioned postmenopausal women
- Diagnosis
  - Tilt table
  - Epinephrine levels

Treatment of POTS

- Drinking more water
- Avoiding alcohol
- Eating frequent, smaller, high CHO meals
- Increasing salt intake and caffeine
- Exercise
- Fludrocortisone
- Beta blockers
- Midodrine
- SSRI/SNRI/Stimulants/Anti-anxiety agents
- Continuous oral contraceptives

Treatment of the 55 yr old

- 64 ounces water daily
- Limit caffeine to 12 ounces
- Walking 5 minutes, gradually increasing to 30 minutes per day
- By week 2, resolved
Migraine and Dizziness Associated with Comorbid Psychiatric Disorders

- Migraine comorbidities exist with major depression and panic disorder
- Migraine is a risk factor for both
- Dizziness is the second most common symptom of panic attacks after depression
- Panic and anxiety patients have an increased rate of vestibular test abnormality
- Risk or cause

Dizziness due to anti-migraine medication

- Dizziness is a common side-effect of migraine medications
- Elicit detailed drug history
- Establish onset of dizziness in relation to medication changes
- Anti-hypertensive agents
- Tricyclic antidepressants
- Anti-epileptic drugs

Case of a 47 Year Old Episcopalian Priest

- Referred by neuro-otologist with sudden onset of severe vertigo and nausea while serving communion
- Subsequent mild bi-frontal headache lasting <6 hrs
- Recurrent episodes x 2, both severe
- MRI normal, abnormal ENG, hearing normal

On Interview

- Childhood motion sickness
- Migraine attacks in late adolescence and his early 20s
- Family history of migraine
- Mild migraine attacks, 2 per month, never diagnosed or treated (except OTCs)

Diagnosis - Migraine with aura (IHS)

- Vertigo as symptom of migraine aura
- Vertigo < 1 hour
- Preceding mild headache, phonophobia
- Normal exam
- Rx: triptan (pre-service); valproate prophylaxis

Diagnosis - Migraine with aura (IHS)

- Vertigo as aura symptom of moderate severity
- Childhood history of motion sickness
- Migraine first, late vestibular symptoms
- IHS migraine
58 year old Medical Coder

- Sent to neurology in September
- Six month hx of “dizziness”; none prior
- In April, noticed tight sensation across “belly”, then onset of spinning, tinnitus, mild headache, followed by vomiting, presyncope
- No diplopia, no sensory symptoms, no change in chronic tinnitus

Precipitating factors for “spells”

- Spells from onset until vomiting....3 minutes
- If lies down quickly, won’t vomit
- All occur while walking
- Any time she walks > 100ft, she develops severe SOB, then if she doesn’t stop, a spell begins
- Up to four spells/day; now working from home

Initial evaluation for “spells”

- Presented to her internist in April
- Initially thought secondary to weight/heat
- Known hypertension, initial visit BP 148/75
- As episodes continued, sent to ENT, given diagnosis of Eustachian tube dysfunction
- Tx: Astelin and Flonase
- In July, underwent B myringotomy/tube placement
- Helped ear pressure, but no change in spells

Symptoms at time of presentation in neurology

- Fluctuating tinnitus
- Posterior pounding headache
- Short of breath just walking 6-7 feet
- PMH: Type II Diabetes mellitus (HAC 4.6) Hypertension
- Exam: Nystagmus, elevated BMI 52.9 (height 5’9”, wt 228lbs)
- Meds: Synthroid, Metformin
- Exam: Normal cranial nerve exam, nl motor strength, nl sensory exam, nl coordination, DRT’s 1+, Babinski absent, Romberg negative, slight wobble on heel walk, able to toe and tandem walk if only 4-5 feet; severe SOB in 5-6 feet; normal hearing on Weber/Rinne; normal cognition; lying BP 110/70 PM; sitting BP 100/66 P 97
- Standing BP 98/50 P100

Recent evaluations

- MRI of brain showed only ischemic white matter changes
- Cardiac ECHO was normal
- ENT consultation
- Neurology consultation

Differential Diagnosis

- Migrainous vertigo
- Complicated migraine
- Abdominal migraine
- Migraine associated stroke
- Cardiac syncope
- Ischemic labyrinthitis
- ONE SIMPLE TEST?????????
Diagnostic studies

- Complete neurological exam
- Vascular exam
- Cardiac exam
- Laboratory studies:
  - Hematocrit 14.6 (37-47)
  - Hemoglobin 5.0 (12-16)
  - Rbc 1.16 (3.9-5.2)
  - Platelet count 30K
- Last HCT was June of previous year and was 41

Illustrates Importance of HX/Basic Evaluation

- Both ENT and Neuro consults prior to complete blood counts despite hx of syncope
- Features may have mislead
- Dx: Myelodysplastic Disorder

43 year old plant manager March 2008

- Regular day...4pm sudden onset “spinning”, with nausea, wife had to help him walk
- Spinning with R tinnitus, headache
- PCP diagnosed vertigo with headache; BP elevated to 140/100; tx: Toprol

43 year old manager

- Endocrine consultation negative
- Neurology consult: MRI/MRA normal; dx: vestibulopathy; tx: vest exercise; amitriptyline/sumatriptan
- Recalled childhood headaches with exertion
- Syncope one month later; taken to ER BP 147/90
- Cardiologist: stopped all meds; added lisinopril; 24 hour Holter negative

43 year old plant manager

- By May 2008: headache much worse in intensity, EEG nl, ECHO mild LVH
- ENT consult: dx; vestibular neuritis, extended “balance” therapy; tx; OTCs
- August 2008: vertigo worse, headache daily though less intense, not able to work (not a day missed in past 13 years)
- September 2008: bad sinus inf; R hearing loss; 2nd ENT consult dx: Meniere’s Ds; tx: low Na diet, diazepam, HCTZ with some help; back to work Aug-Jan 2009

43 year old manager

- January 2009: disabling vertigo, severe daily headache, severe tinnitus and “syncopal” events
- Spells of incoherence, facial tingling, could answer but nonsensically, photophobic, headache with “knife in eyeballs”, worse on R, throbbing pain with nausea, increased vertigo
- Sleep consult: PSG dx was OSP; mild RLMS
- Epileptology consult: EEG-CCTV showed two non-epileptic spells; told likely childhood maltreatment
43 year old manager April 2009
- DX: Migrainous Vertigo with autonomic features; now chronic migraine
- Tx: candesartan and topiramate
- Triptan/naproxyn for more severe migraine
- Aggressive vestibular therapy
- Elevated homocysteine/positive factor V Leiden: added ASA/B6/folic acid
- High fluid intake encouraged

43 year old manager June 2009
- Between May and June visits: only two mild migraine attacks; pain free in less than one hour
- Only two mild attacks of vertigo, lasting for less than 15 minutes, no associated HA or nausea
- BP 110/82
- Back at work full time

Conclusions
- Associations of vertigo and dizziness are complicated
  - Causal
  - Statistical
  - Coincidental
- Merits further research
- Identify dizzies who may benefit from migraine treatment
- History is paramount

Disclosures
- Allergan
- Merck
- Eli Lilly
- GSK
- Clinvest
Cluster Headache
Rebecca Erwin Wells, MD, MPH
Wake Forest University Baptist Medical Center
Winston-Salem, NC
Assistant Professor of Neurology
Center for Integrative Medicine Associate Director of Clinical Services
rewells@wakehealth.edu

Primary Headache Disorders
• Migraines, tension-type, other
• Trigeminal Autonomic Cephalalgias (TACs)
  – Lateralization
  – Ipsilateral autonomies
  – Frequency/duration/severity differs
    • Cluster vs. Migraine/tension-type
    • Cluster vs. other TACs

Why is Cluster Diagnosis so Important?
• Secondary causes to rule out
• Gives clarity to patient
• Treatment
• Severity: Suicidal

Objectives
• By the end of this talk, you will feel confident in:
  – Recognizing cluster headache
  – Diagnosing cluster headache
  – Treating cluster headache
• Stimulate your curiosity, compassion

Misdiagnosis
• 1st attack to diagnosis
  – Range: 1 wk to 48 yrs!
  – Average: 7 Years!
• >4 doctors seen prior to diagnosis
  – Dentist (34%) or ENT (33%) 1st
• 16% underwent tooth extraction

Klapper et al. Headache 2000
This patient tells you...

- Video 1

ICHDI-II Diagnostic Criteria

3.1 Cluster HA

A. At least 5 HA attacks
B. HA features:
   - Severe/very severe
   - 15 min to 3 hours
   - Strictly unilateral orbital, supraorbital/temporal
C. At least 1 (ipsilateral):
   - Conjunctival injection/lacrimation
   - Nasal congestion/rhinorrhea
   - Forehead and facial sweating
   - Miosis and/or ptosis
   - Eyelid edema
   - Restless/agitation
D. One qod to 8/day
E. Not attributed to another disorder

Cranial Autonomic Features of Attack

Another patient tells you...

- Video 2

Definitions

- Attack or Cluster HA
  - Individual episode: min-hrs
- Cluster Period or Cluster Bout
  - Series of attacks: wks-mo
- Remission
  - Pain free period: mo-yrs

Nestoriot A D, Goadsby P J BMJ 2012;344:e40407

© 2012 by British Medical Journal Publishing Group

Nesbitt A D, Goadsby P J BMJ 2012;344:e2407
And he describes the picture…

- Video 3

Additional Features-Attacks

- Pain
  - Maximal at one spot, but may spread
  - Abrupt onset, ending
  - Excruciating

- Agitation, restlessness

- Circadian periodicity
  - “Alarm clock HA”

Additional Features-Bouts/Periods

- Circannual periodicity

- Triggers during cluster period (and in chronic):
  - alcohol, sleep, histamine, nitroglycerine

Epidemiology

- 0.1% in population
- Males 3-4 x’s
- 20-40 yo onset
  - average: 28yo

Interesting aspects

- Behaviors: smoking, drugs, alcohol, high risk
- Comorbidities: OSA
- Genetics-5% may be inherited
- Pathophysiology
  - Ipsilateral hypothalamus
  - Autonomies, circadian rhythm
The Trigeminovascular Reflex.

Stop the BOUT*

- Verapamil*
  - Start 40-80mg bid, likely higher
  - EKG: baseline, dose changes, 6mo routine
  - JUST during bout

- Lithium* 600-1200mg/day (0.7-1.2 level)
- Prednisone taper*
- Greater occipital nerve block*
- Melatonin*, Topiramate,* (methylsergide*)

Differential/Evaluation

- Other HA
  - Hypnic, different TAC, TN, migraine
- Intracranial lesion
  - Pituitary, vascular, infectious, neoplastic
- Dental, sinus

- MRI brain (pituitary) with contrast
  - Atypical history
  - Abnormal neuro exam

Stop the ATTACK

- Injectable Sumatriptan (SQ)
  - 2 doses of 6mg/day, given enough
  - ONLY FDA approved

- Oxygen*, 100% (*smoking danger)
  - 12-15L/min with non-rebreather face mask
  - At onset for 15-20 minutes

- NS Sumatriptan* 20mg, NS zolmitriptan* 5mg

Treatment-Dramatic Difference

- Video 4, 5

General Principles of Therapy

- Treat immediately (SQ, not oral!)
- Begin prophylactics ASAP with bout
- D/C prophylactics-bout over
- Adequate doses
- Monitor closely, adjust accordingly
- Educate patient-condition, options
Triptans: Contraindications

- Ischemic disease (history/multiple risk factors)
  - Cardiac, peripheral, cerebrovascular
  - Coronary vasospasm (including Prinzmetal’s)
- Uncontrolled HTN
- Hemiplegic/basilar migraine
- Severe hepatic impairment

Summary Tips

- Think Cluster when:
  - Lateral, V1, excruciating, autonomic, cyclical, pacing
- Treat immediately: critical
- Rule out other causes (esp. pituitary)
- Address OSA, smoking
- Follow closely-bouts, annually

Prophylactic Comparisons

- Indications
  - Migraine/TTH ≥ 1/wk, abortives not working
  - Cluster: nearly everyone, but only during bout
- Goals
  - Migraine/TTH: Decrease freq/severe/duration
  - Cluster: Eliminate!

Objectives

- By the end of this talk, you will feel confident in:
  - Recognizing cluster headache
  - Diagnosing cluster headache
  - Treating cluster headache
- Stimulate your curiosity, compassion

If Refractory

- Neuroimaging
- Other diagnoses
- Increase/change/add meds
- Potential treatment considerations*
  - Neurostimulators*, DBS*
  - “Clusterbusters.com”*
  - Surgery* last option

Acknowledgements

- Elizabeth Loder, MD, MPH
- Patients
- Southern Headache Society
- Thank you
Any Questions?

rewells@wakehealth.edu
Highlights of Headache Research 2012
Morris Maizels MD
Blue Ridge Headache Center
Asheville NC

Overview

- Practice-changing
  - Efficacy data demonstrate efficacy for migraine
  - Aspirin avoidance line therapy
  - Botox/dysfunction use correlates with MCG
- Mind-Changing
  - Migraine is a “whole brain” disorder
  - Migraine displays increased attention to pain modulation
  - Migraine changes the brain (neuroplasticity)
- Lessons from psychiatry
  - Botulinum toxin improves depression
  - Behavioral medicine
    - Anxiety sensitivity predicts headache trigger
    - “Refactory” suggests possible personality disorder
- Interventions
  - Pericranial nerve blocks
  - OMT update
  - Plastic surgery
  - Bariatric surgery

Criteria for Article Selection

- Articles of general interest with appropriate methodology which:
  - Advance, shift, or challenge our knowledge or practice
  - May illustrate flaws or fallacies in assumptions underlying evidence-based medicine
- Focus is on migraine

Neurology 2012: 530-543

- 2 replicate RDBPCT, crossover, 3-attack studies compared
  - Treximet to BAC for the acute treatment of the moderate-to-severe pain phase of a migraine attack,
  - No statistically significant difference for the primary endpoint of sustained pain freedom 2 to 24 hours
    - Differences for both active treatment groups compared to placebo were statistically significant.
  - Treximet was statistically superior to BAC and placebo at nearly all timepoints for pain-freedom and migraine-freedom.
  - Treximet > BCM for first and second rescue medication use and to placebo for first rescue medication use.


“Generally, the results for Fioricet were very disappointing, and it remains an enigma why 88% of these patients were satisfied with BCMs.”

Additional Efficacy Results
(unpublished data courtesy of GSK)

<table>
<thead>
<tr>
<th></th>
<th>Trex</th>
<th>Trex</th>
<th>BCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>317</td>
<td>304</td>
<td>320</td>
</tr>
<tr>
<td>Placebo vs</td>
<td>vs</td>
<td>vs</td>
<td>vs</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>P</td>
</tr>
<tr>
<td>2-hr P-Relief</td>
<td>148 (48%)</td>
<td>114 (39%)</td>
<td>76 (25%)</td>
</tr>
<tr>
<td>4-hr P-Relief</td>
<td>124 (40%)</td>
<td>90 (30%)</td>
<td>51 (17%)</td>
</tr>
<tr>
<td>2-hr P-Free</td>
<td>45 (14%)</td>
<td>26 (8%)</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>4-hr P-Free</td>
<td>86 (27%)</td>
<td>59 (19%)</td>
<td>21 (7%)</td>
</tr>
<tr>
<td>2-hr Mgr-Free</td>
<td>83 (10%)</td>
<td>22 (7%)</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>4-hr Mgr-Free</td>
<td>74 (23%)</td>
<td>37 (12%)</td>
<td>20 (6%)</td>
</tr>
</tbody>
</table>
**Personal interpretation of data**

- Primary outcome measure may be too strict
- Sumatriptan-naproxen is clearly superior to BCM for all outcomes (except the primary)
- BCM is clearly superior to placebo for pain-relief and less so for pain-freedom
- Outcomes were less than typically reported for triptans
- Would 2x BCM have increased efficacy?
- Might the risk of MOH be related to the frequency of allowed use?
- Why do patients report satisfaction with BCM?
- Does psychiatric status predict satisfaction with BCM?

**Conclusions re BCM**

- This is the only RDBPCT of BCM for migraine, and it clearly shows efficacy
- The debate is no longer whether BCM is effective; rather,
  - What is its place in migraine therapy?
  - Do the risks outweigh the benefits?
  - Who should receive BCM?
  - What quantities are likely to be “safe?”
  - Should Rx of BCM be limited to specialists?

**Aspirin is First-Line Treatment for Migraine and Episodic Tension-Type Headache Regardless of Headache Intensity**

* Lampl, Voelker, Steiner. *Headache* 2012;52:48-56

**Background.**

Stratified care chooses between symptomatic therapy and triptans as first-line on an individual basis according to perceived illness severity.

We questioned the 2 assumptions underpinning stratified care in migraine that greater illness severity: (1) reflects greater need; and (2) is a risk factor for failure of symptomatic treatment but not of triptans.

**Aspirin with or without an antiemetic for acute migraine headaches in adults.** Kirthi V, Derry S, Moore RA, McQuay HJ. *Cochrane Database Syst Rev.* 2010.

- Thirteen studies (4222 participants) compared:
  - Aspirin 900 mg or 1000 mg, alone or in combination with metoclopramide 10 mg, with:
    - placebo or
    - other active comparators, mainly sumatriptan 50 mg or 100 mg.
- Sumatriptan 50 mg did not differ from aspirin alone for:
  - 2-hour pain free or headache relief
- Sumatriptan 100 mg > aspirin plus metoclopramide for:
  - 2-hour pain-free
  - not headache relief

**AUTHORS’ CONCLUSIONS:**

Aspirin 1000 mg is an effective treatment for acute migraine headaches, similar to sumatriptan 50 mg or 100 mg.


- Effervescent ASA (1000 mg) was compared to encapsulated sumatriptan (50 mg), ibuprofen (400 mg) and placebo.
- Primary endpoint - reduction in headache severity from moderate or severe to mild or no pain was:
  - ASA 52.5%
  - Ibuprofen 60.2%
  - Sumatriptan 55.8%
  - Placebo 30.6%
- All active treatments were superior to placebo (P < 0.0001), whereas active treatments were not statistically different.
Meta-comments on BAC, ASA, and triptans

- Investigator bias can
  - use methodology to influence results
  - influence reporting and interpretation of data
  - lead to "evidence-based guidelines" that may not be truly objective

Risk factors for MOH (continued)
Multivariate analyses

- 5-fold increased risk for developing MOH among individuals who at baseline:
  - reported regular use of tranquilizers; or
  - had a combination of chronic musculoskeletal complaints, gastrointestinal complaints, and Hospital Anxiety and Depression Scale score >21
- Smoking and physical inactivity more than doubled the risk of MOH.
- In contrast, these factors did not increase the risk of CDHwoO, suggesting these are pathogenetically distinct.

Basic Science Highlights

- Migraine is a whole brain disorder
- The migraine brain displays altered interictal pain processing dynamics
- Migraine changes the brain (neuroplasticity)

CNS Activation During Migraine

Dysfunction of brain stem pain and vascular control centers

Pain Perception*
- Anterior cingulate cortex

Migraine Generator*
- Raphe nuclei
- Locus coeruleus
- Periaqueductal gray

*Areas of red indicate cerebral blood flow increases (P < 0.001).
(Weiller et al. 1995)

Neurovascular theory of Migraine

Goadsby 2000.

Methods.
• Resting-state functional MRI
• Compared functional connectivity between PAG and brain areas involved in pain processing and modulation.
• Assessed the relation between intrinsic resting-state correlations within PAG networks and the average monthly frequency of migraine attacks, as well as allodynia.
  ➢ 17 subjects with migraine, cf 17 gender- and age-matched controls during a pain-free state.

PAG connectivity - Results
• Stronger connectivity between the PAG and several brain areas within pain processing pathways in migraineurs versus controls.
  – midbrain, thalamus, PFC, ACC
• With increase frequency of migraine attacks:
  – increased connectivity in pain processing areas
  – decreased connectivity in pain modulating areas:
    • PFC, ACC, amygdala
• Migraineurs with allodynia -significantly reduced connectivity between PAG, prefrontal regions, and ACC

PAG - Interpretation
Results suggest interictal dysfunctional dynamics within pain pathways in migraine manifested as an impairment of the (cortical) descending pain modulatory circuits, likely leading to loss of pain inhibition, and hyperexcitability primarily in nociceptive areas.


Purpose.
• Defining concurrent functional and structural cortical alterations may provide specific insights into the unfolding adaptive or maladaptive changes taking place in cortex in migraine.
Cortical changes - Methods

• Using hrMRI, structural and functional cortical measures were compared in:
  – high frequency (HF; 8–14 days/month; n=10), to
  – low frequency (LF; <2 days/month; n=10) attacks, and to
  – healthy controls (HC; n=20).

Cortical changes - Results

• HF patients
  – greater thickness in the post-central gyrus (face), which correlated with the stronger functional activation
  – smaller cortical volume in the cingulate cortex that correlated with lower activation
• Similarly significant structural and functional differences (HF>LF) in the insula that may reflect potential alteration in affective processing.


Methods.
• Using voxel-based morphometry, structural MRIs were compared between 29 patients with MOH and migraine, and healthy controls.

Gray-matter/MOH - Results

• In all (29) patients a significant increase of grey matter volume (GMV) was found in the periaqueductal grey
  – correlated positively with:
    • MIDAS
    • HADS anxiety subscale
• GMV increase also found bilaterally in the thalamus, and the ventral striatum.
• GMV decrease in frontal regions including: orbitofrontal cortex, anterior cingulate cortex, the left and right insula, and the precuneus.

Gray matter/MOH – Implications

• Results suggest dysfunction of antinociceptive systems in MOH, which is influenced by anxiety.
• Increased GMV might reflect increased facilitation of sensory input
• Neurobiological similarities between MOH and substance abuse disorders have been proposed
  – PET study found hypometabolism in OFC which persisted after withdrawal of substance causing MOH
• Dysfunction of the reward system may be a neurobiological basis for dependence in a subgroup of MOH patients.


Background.
• Hippocampus is involved in:
  – memory consolidation/spatial navigation
  – stress response
    • inhibitory feedback to HPA
    • hippocampus is affected by stress, glucocorticoids, excitatory AAs
• Migraine attacks are repeated stressors; alterations in hippocampal function and structure may play an important role in migraine pathophysiology
Hippocampus and Migraine - Methods

- Using hMRI, hippocampal morphometric and functional differences (in response to noxious heat stimulation) were compared in:
  - age and gender-matched
  - acute episodic migraineurs
  - high (HF) versus low (LF) frequency of migraine attacks, cf healthy controls (HC).

Hippocampus and Migraine – Results

- Significant larger bilateral hippocampal volume was found in LF cf HF and HC groups.
- Functional correlates of greater deactivation in the same hippocampal regions (in response to noxious stimulation) was also accompanied by overall reduction in functional connectivity of the hippocampus with other brain regions involved in pain processing in the HF group.

Hippocampus and Migraine – Implications/Discussion

- Larger hippocampal volume in LF group cf HF and HC groups suggests an initial adaptive plasticity that may then become dysfunctional with increased frequency.
- Increased levels and activity of chemical mediators, under prolonged stress, may alter hippocampus
  - structurally (regeneration of neurons, loss of synapses)
  - functionally (abnormal level of neurotransmitters, impaired inhibition)
- Initial changes may be adaptive to maintain homeostasis in the face of new challenges or stressors

Hippocampus and Migraine – Discussion (cont’d)

- growing support for the concept of hippocampus being involved in pain processing
- recent imaging studies of pain in humans report hippocampal activation in a variety of conditions
  - such activation may be associated with processing related to anxiety.
- Amplifies aversive effects as a protective mechanism to define appropriate behavioral responses.

Summary of cortical studies

- PAG
  - decreased connectivity in pain modulating areas (PFC, ACC, amygdala) with:
    • increased frequency of migraine attacks
    • allodynia
- MOB
  - increased GMV in PAG, correlating w
    • MDA
    • anxiety
  - GMV decreased in limbic regions (PFC, ACC, insula, precentral).
- Hippocampus - reduced functional connectivity with other brain regions involved in pain processing in high frequency migraineurs

Neurolimbic model of migraine
(from Maizels, Aurora, Heinricher. Headache Oct 2012)
Immortality only 20 years away. Ray Kurzweil. The Telegraph

Scientist Ray Kurzweil claims humans could become immortal in as little as 20 years’ time through nanotechnology and an increased understanding of how the body works.

Lessons from psychiatry


- Negative emotions, like anger, fear, and sadness, that are prevalent in depression are associated with activation of the corrugator and procerus muscles in the glabellar region of the face.
- In patients with depressive disorders, facial EMG reveals a relative overactivity of the corrugator muscles during different affective imagery paradigms.
- Facial feedback hypothesis
  - mutual interaction between emotions and facial muscle activity (Darwin, 1872; James, 1890)
  - “Refuse to express a passion, and it dies” (William James 1890)

Treatment of the glabellar region with botulinum toxin influences emotional experience

- a relative change in facial expression from angry, sad, and fearful to happy
- individuals report an increase in emotional wellbeing beyond the cosmetic benefit (Sommer et al., 2003).
- reduced levels of fear and sadness were observed (Lewis and Bowler, 2009).
- attenuated activation of limbic brain regions during voluntary contraction of the corrugator and procerus muscles, indicating that feedback from the facial musculature may modulate the processing of emotions

Botulinum for depression. Methods

- Investigator initiated and carried out independently of any commercial entity.
- Inclusion criteria
  - age 25-65 years,
  - current major depressive disorder (DSMIV)
  - stable antidepressant treatment
  - a moderate to severe vertical glabellar line during maximum voluntary frowning according to a 4-point clinical severity score (Honeck et al., 2003)
- Exclusion criteria
  - regular occurrence of migraine or other forms of "cachexia."
- Intervention
  - Women received 25 U of onabotulinum toxinA in total.
    - 7 U to the procerus
    - 6 U bilaterally to the medial part of the corrugator muscles,
    - 5 U bilaterally to the lateral part of the corrugator muscles.
  - Men received two more units at each injection site, i.e. 39 U in total.
- To control cosmetic changes from psychometric rated, participants wore an opaque surgical cap, which covered glabella and forehead during the examinations.

Botulinum for depression. Results

- Primary end point (HAM-D17 after six weeks versus baseline)
  - significant improvement compared to placebo, with a large effect size: [-10.1 +/- 8.2 points, 47.3% vs. -1.73 +/- 4.25 points, 9.2%] ANOVA, Student’s t-test, n = 30; F[1,28] = 12.30
- Response rate >/= 50% HAM-D17 score reduction; 
  - 60.0% vs. 13.3% OR 9.8, 95%CI 1.6-59.7 p = 0.02
- Even larger effect sizes were observed at the end of the sixteen-week follow-up
- Treatment response was not associated with the appraisal of the cosmetic change (as positive)
Botulinum for depression.
Possible mechanisms

- Reduced proprioceptive feedback from frown muscles
- May act comparable to a passive and uninterrupted relaxation exercise.
- ? improved feedback from social interaction partners
- ? central pharmacological effect (retrograde axonal transport)
  — Substance P

Botulinum for depression.
Limitations of study

- At the end of the trial 90% of the participants guessed their group allocation correctly with firm conviction (based on cosmetic appearance).
- However, treatment expectancy and rationale credibility ratings did not differ between groups at baseline and did not predict clinical outcome.

Lessons from Behavioral Medicine

Anxiety Sensitivity and Headache Triggers.
A. Brooke Walters, Timothy T. Houle, Joshua D. Hamer, & Todd A. Smitherman
(AHS 2012)

Anxiety Sensitivity as a Predictor of Headache Frequency and Disability among Individuals with Episodic Migraine and Tension-Type Headache.
Rachel E. Davis & Todd Smitherman
(AHS 2012)

Anxiety Sensitivity

- Anxiety sensitivity (AS) is the fear of benign physical sensations that develops from beliefs that these sensations have harmful physical, cognitive, or social consequences (Taylor et al., 2007).
  - physical concerns (e.g., heart palpitations signify an impending heart attack)
  - cognitive concerns (e.g., trouble thinking clearly leads to insanity)
  - social concerns (e.g., others will notice my anxiety and display rejection or ridicule).
- AS has been found to be a strong predictor of fear of pain and avoidance behaviors among individuals with headache

Anxiety Sensitivity

- Higher AS correlates w:
  — greater # triggers
  — Frequency of encountering most important trigger (ASI-PC, ASI-SC)
  — Headache probability after exposure (ASI-PC)
Anxiety Sensitivity predicts headache frequency and disability

Table 2. Linear Regressions Predicting Headache Variables as a Function of ASI3 Total Scores

<table>
<thead>
<tr>
<th>Criterion Variable</th>
<th>β</th>
<th>R² change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine with Aura</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache Frequency</td>
<td>-21</td>
<td>10.9%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Headache Severity</td>
<td>15</td>
<td>2.9%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Headache-Related Disability</td>
<td>21</td>
<td>4.3%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Migraine without Aura</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache Frequency</td>
<td>-22</td>
<td>3.2%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Headache Severity</td>
<td>18</td>
<td>3.2%</td>
<td>.08</td>
</tr>
<tr>
<td>Headache-Related Disability</td>
<td>16</td>
<td>1.8%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Daily and near-daily headache and Personality Disorder.
Jevoux, Cymchantowski
(Rio de Janeiro, Brazil – AHS 2012)

- 45 patients at a tertiary headache center with CM and/or MOH and PD (histronic, borderline, or other).
- at 4 months, 91% showed no response to usual care.
  > Implication: label of “refractory” should engender a search for something more than another drug or a stimulator trial.
  > Conversely: refractory pain often leads to regressive and maladaptive coping behavior
  > “If drugs don’t work, try something else.”

Interventional Therapies

- Pericranial nerve injections
- Occipital nerve stimulation
- Plastic surgery
- Bariatric surgery

Management of Chronic Migraine with Quarterly Pericranial Nerve Blocks: A Prospective 48-week Trial.
Robert Kaniecki. U Pittsburgh (AHS Abstract)

- Methods
  - Administration of pericranial injections
  - 12-week intervals
  - 4 sets of injections over 48 weeks
  - Fixed-dose (0.1 cc of 0.25% bupivacaine)
  - Fixed-site (17 pericranial nerve injections each side)
  - 10 injections: Greater and lesser occipital
  - 5 injections: Auriculotemporal and stylogmaticotemporal
  - 2 injections: Supraorbital and supratrochlear

Results

- 218 subjects enrolled and treated

<table>
<thead>
<tr>
<th>Baseline Characteristics (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>History of migraine (years)</td>
</tr>
<tr>
<td>Headache days per 4 weeks</td>
</tr>
<tr>
<td>Severe headache days per 4 weeks</td>
</tr>
<tr>
<td>Acute treatment days per 4 weeks</td>
</tr>
<tr>
<td>HIT-6 score</td>
</tr>
</tbody>
</table>
Results

• 116 subjects (53.2%) met the primary endpoint with >50% reduction from baseline in monthly frequency of headache days at 48 weeks
  – 77 subjects (35.3%) with response < 4 weeks
  – 25 subjects (11.5%) with no response or lost to follow-up

Results – Responder subgroup analysis (n=116)

– Mean monthly headache days: 22.8 -> 9.0
– Mean monthly severe headache days: 15.9 -> 6.1
– Mean monthly acute treatment days: 18.1 -> 7.9
– Mean HIT-6 score: 66.7 -> 59.2
– No clinical or demographic differences versus the nonresponder subgroup

Results - responders


Methods.

• Crossover trial of rFCM patients who responded to stimulator trial.
  – failed/intolerant 2 preventives
  – off preventives at time of trial

Results.

• 30/31 responded to trial
• Median headache days: 25 -> 6 (p<.001)
• MIDAS – 79 -> 19 (3 mo) -> 10 (6/12mo)


• largest RDBPCT to date
  – 122/125 completed 12-week trial
• No difference in the primary endpoint (50% reduction in VAS)
• Significant difference with:
  – 30% reduction in VAS
  – total number of headache days, QOL, satisfaction with treatment, etc.

Comments re interventional trials

• Widely varying definitions of “refractory”
• Lack of non-pharmacologic therapies for definition of refractory
• Adequate control groups

Methods.
- Retrospective chart review of 253 patients who underwent surgery for frontal migraine
  - transpalpebral nerve decompression (n = 62)
  - endoscopic nerve decompression (n = 191).

Results.
- "Successful outcome" 49/62 patients (79%) transpalpebral cf 170/191 (89%) endoscopic (p<0.05)
  (p=50% decrease in migraine frequency, duration, or intensity)
- Complete elimination of migraine headaches 32 (52%) transpalpebral cf 128 (67%) endoscopic (p<0.05)


Methods.
- Patients were randomly assigned to receive either actual or sham surgery in their predominant trigger site.

Results.
- 50% reduction in migraine headache 
  - sham surgery - 15 of 26 (57.7%) cf actual surgery - 41 of 49 (83.7%) (p < 0.05)
- Complete elimination of migraine 
  - 1/26 (3.8%) (sham) cf 28/49 (57%) (true) (p < 0.001).

Issues with plastic surgery studies of migraine
- Only one investigator has reported results
- Questions re randomization, blinding, outcome measures
- Why the resistance in the headache community to this literature, compared with botulinum, PFO, GON blocks,...?


Methods.
- 125 patients randomized - 100 true, 25 control

Results.
- 89/100 underwent surgery 
  - 19 were followed for 5 years
  - 25 underwent deconstruction of additional (different) trigger sites during the follow-up period and were not included in the data analysis (7)
- 54/89 (60.7%) = response of 5 years 
  - 10/89 (11.2%) = complete elimination of migraineheadache
  - 44 (54%) = significant decrease
  - 8 (10%) = no significant change
  - All measured variables at 6 months improved significantly (p < 0.001).


Background.
- The objective of this study was to build on previous studies to illustrate implementation of a "publication strategy" by the drug manufacturer for four off-label uses of gabapentin (Neurontin®): PNS, Inc.; migraine prophylaxis, treatment of bipolar disorders, neuropathic pain, and nociceptive pain.

Methods.
- We included in this study previously undisclosed internal company documents, email correspondence, memorandum, study protocols and reports that were made publicly available in 2008 as part of litigation brought by consumers and health insurers against Pfizer for fraudulent sales practices in its marketing of gabapentin.
- reviewed documents pertaining to 21 clinical trials, 12 published.
  - 3 trials each for migraine prophylaxis and bipolar disorders
  - 9 trials for neuropathic pain
  - 6 for nociceptive pain

Results.
- 21 trials sponsored by Pfizer and Parke-Davis: 
  - 3 trials each for migraine prophylaxis and bipolar disorders
  - 9 trials for neuropathic pain
  - 6 for nociceptive pain
Neurontin litigation (continued)

Results
• 21 trials sponsored by Pfarr and Parke-Davis:
  -- Trials for migraine prophylaxis and bipolar disorders
  -- Trials for neuropathic pain
  -- Trials for spinchter pain
• We present extracts from internal company marketing assessments recommending
  that Pfarr and Parke-Davis (Pfarr acquired Parke-Davis in 2000) adopt a
  "publication strategy" to conduct trials and disseminate trial findings for
  unapproved uses rather than an "indication strategy" to obtain regulatory
  approval.
  -- Publication content was influenced and "spin" was applied
  -- the company selected where trial findings would be presented or published
  -- publication of study results was delayed
  -- the role of ghost authorship.

Neurontin litigation (continued):
“Marketing assessment” for migraine prophylaxis

• recommended a publication strategy, to ‘conduct
  only publication study(ies) in the U.S.,’ and in a
  manner comparable to what was described for
  bipolar disorders and neuropathic pain, to
  publish the results, ‘iff positive.’
• also stated ‘an indication strategy cannot be
  justified since an NDA (New Drug Application)
  filing would occur close to patent expiration.’

Neurontin litigation (continued)

Conclusions
• Internal company documents illustrate
  implementation of a strategy at odds with
  unbiased study conduct and dissemination.
• "Publication strategy" had the potential to
  distort the scientific literature, and thus
  misinform healthcare decision-makers.

What I’ve learned from 2012

• Expanding role for non-triptan therapies
• Functional imaging suggests:
  -- Migraine is a whole-brain disorder
  -- the interictal migraine brain is abnormal
  -- Migraine changes the brain (neuroplasticity)
• Psychiatric effects of migraine therapies should be
  accounted for (botulinum toxin)
• Behavioral factors may underlie susceptibility to
  conventional headache triggers
• Broad range of interventional therapies may have a role
  for migraine
• EBM may reflect bias at many levels