Challenging Cases – AHS Scottsdale

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As of 1/1/17

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## Disclosures 2016

**Stewart Tepper, MD**

<table>
<thead>
<tr>
<th>Category</th>
<th>Companies/Institutions</th>
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| **Grants/Research Support**     | • Alder  
• Allergan  
• Amgen  
• ATI  
• Avanir  
• Teva  
• Zosano |
| **Consultant:**                 | • Acorda  
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• Amgen  
• ATI  
• Avanir  
• Kimberly-Clark  
• Pernix  
• Pfizer  
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• Kimberly-Clark  
• Scion Neurostim  
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• Teva  
• Pfizer |
| **Stock options:**              | • ATI |
| **Royalties:**                  | • University of Mississippi Press  
• Springer |
| **Salary**                      | • American Headache Society |
## Disclosures 2016

### Lawrence Newman, MD

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Objectives

• We will present challenging cases and ask for help
• At the end of the presentation, we hope that you will have clues as to differential diagnosis, work up, and treatment of varying, vexing headache disorders
• If you brought cases, we would like to start with those first, so let us know
• Don’t be shy with questions at any point
Trigeminal Autonomic Cephalalgias (TACs) and Other Primary Headaches

TACs

3.1 Cluster [CH]
   (3.1.1 Episodic; 3.1.2 Chronic)
3.2 Paroxysmal hemicrania (3.2.1 Episodic, EPH); 3.2.2 Chronic, CPH)
3.3 Short-lasting unilateral neuralgiform headache attacks (SUNHA)
   3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), Episodic & Chronic
   3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), Episodic & Chronic
3.4 Hemicrania continua [HC] (remitting and unremitting)

Other Primary HAs

4.1 Primary cough headache
4.2 Primary exercise headache
4.3 Primary headache associated with sexual activity
4.4 Primary thunderclap headache
4.5 Cold-stimulus headache
4.5.1 Headache attributed to external application of a cold stimulus
4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus
4.6 External-pressure headache
4.6.1 External-compression headache
4.6.2 External-traction headache
4.6.3.2 Probable external-traction headache
4.7 Primary stabbing headache
4.8 Nummular headache
4.9 Hypnic headache
4.10 New daily persistent headache (NDPH)
Case 1- A man with explosive headaches

- 65 year old man with onset of explosive headaches
- These occur when he coughs, sneezes, valsalvas
- They generally last only seconds
- He is taking excessive amounts of ibuprofen
- Exam is normal, but he did have an upper respiratory illness with cough prior to the onset of these headaches
What is the diagnosis?

1- Secondary headache: Unruptured aneurysm or sentinel bleed
2- Secondary headache: Posterior fossa mass
3- Cough headache
4- Primary stabbing headache
5- Primary thunderclap headache
What is the diagnosis?

1- Secondary headache: Unruptured aneurysm or sentinel bleed
2- Secondary headache: Posterior fossa mass
3- **Cough headache**
4- Primary stabbing headaches
5- Primary thunderclap headache
What workup would you do?

1- Chest X-Ray for the cough
2- CT and LP for bleed
3- MRI for posterior fossa lesion
4- MRA for aneurysm
5- MRV for cortical vein thrombosis
6- Study of pulses and vascular study for rib compression to look for thoracic outlet syndrome
What workup would you do?

1- Chest X-Ray for the cough
2- CT and LP for bleed
3- MRI for posterior fossa lesion
4- MRA for aneurysm
5- MRV for cortical vein thrombosis
6- Study of pulses and vascular study for rib compression to look for thoracic outlet syndrome
Workup of cough headache

• MRI with a careful look at the posterior fossa
• Secondary causes for cough headache occur at least \textbf{40\% of the time}, usually \textbf{Chiari I}
• Aneurysms, posterior fossa tumors and cysts with mass effect, diseases of carotid or vertebrobasilar arteries can also cause secondary cough headaches, which is why the MRA is needed
ICHD-3 Primary Cough Headache

A. At least two headache episodes fulfilling criteria B- D

B. Brought on by and occurring only in association with coughing, straining and/or other Valsalva maneuver

C. Sudden onset

D. Lasting between 1 second and 2 hours

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

### Treatment of primary cough headache (no Chiari) - Raskin

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin</th>
<th>LP</th>
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<tbody>
<tr>
<td>N</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Gender</td>
<td>13 M, 3 F</td>
<td>11 M, 3 F</td>
</tr>
<tr>
<td>Age</td>
<td>29-69</td>
<td>33-72</td>
</tr>
<tr>
<td>Response</td>
<td>10 complete, 4 moderate improvement, 2 no response (10-14/16)</td>
<td>6 complete in 2d, 1 recurrence in 6 wks, Repeat LP, complete response, 8 no response (6/14)</td>
</tr>
<tr>
<td>Follow up</td>
<td>3-12 years</td>
<td>3-14 years</td>
</tr>
</tbody>
</table>

Raskin NH. Neurology 1995; 45;1784.
Other treatments of cough headache

- Acetazolamide\(^1\)
- Methysergide\(^2\)
- Metoclopramide\(^3\)

Cough Headache Clinical Pearls

• First and foremost, **eliminate secondary causes**!
• Indomethacin can successfully treat secondary cough headaches, so beware!
• Primary cough headache generally occurs over the age of 40
• **The younger the patient, the greater the concern for secondary causes**
• The use of a daily NSAID is frequently seen in patients with indomethacin-responsive syndromes
## Primary vs Secondary

<table>
<thead>
<tr>
<th></th>
<th>Cough</th>
<th>Exertion</th>
<th>Sex</th>
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<tbody>
<tr>
<td></td>
<td>1º/2º</td>
<td>1º/2º</td>
<td>1º/2º</td>
</tr>
<tr>
<td>Sex: % male</td>
<td>77/59</td>
<td>88/43</td>
<td>85/100</td>
</tr>
<tr>
<td>Age, mean</td>
<td>67/39</td>
<td>24/42</td>
<td>41/60</td>
</tr>
<tr>
<td>Dx</td>
<td>Benign/Chiari I</td>
<td>Benign/ SAH, sinusitis, brain mets</td>
<td>Benign/ SAH</td>
</tr>
<tr>
<td>Rx</td>
<td>Indomethacin Surgery</td>
<td>Ergot propranolol</td>
<td>Indomethacin propranolol</td>
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Case 2- A 65 year old woman comes in with disturbed sleep due to headaches

- For the past 2 months, almost every night, around 2 AM, she is awakened from sleep by headache
- The headaches are dull, mild to moderate, anterior, and bilateral
- She gets up, walks around, and the headache remits in about an hour
- She gets mild nausea, but no autonomic symptoms
What is the diagnosis?

1. Episodic Paroxysmal Hemicrania (EPH)
2. Episodic cluster
3. Hypnic Headache
4. Hemicrania continua (HC)
5. Probable secondary headache
What is the diagnosis?

• 1- Episodic Paroxysmal Hemicrania (EPH)
• 2- Episodic cluster
• 3- Hypnic Headache
• 4- Hemicrania continua (HC)
• 5- Probable secondary headache
What is the workup?

- MRI and sed rate
- CT
- MRV
- Thyroid function tests
What is the workup?

- MRI and sed rate
- CT
- MRV
- Thyroid function tests
Workup for Hypnic Headache

- MRI with and without contrast
- Tumor and a case of CSF leak have both been reported to cause secondary hypnic headaches
- A sed rate for Giant Cell arteritis should be drawn (new onset of headache in an older patient)
ICHD-3 Hypnic Headache

A. Recurrent headache attacks fulfilling criteria B-E
B. Developing only during sleep, and causing wakening
C. Occurring on 10 days per month for >3 months
D. Lasting 15 minutes and for up to 4 hours after waking
E. No cranial autonomic symptoms or restlessness
F. Not better accounted for by another ICHD-3 diagnosis
Hypnic Headache: 40 patients Clinical Characteristics

- Mean age of onset: 62 years old
- 80% female
- 60% bilateral and 65% sharp quality
- 57% severe intensity
- Nausea, photophobia in 22%
- Average frequency: 21/30 nights/month
- Average duration: 186 minutes (3 hours)
- 20% had previous history of migraine

Hypnic Headache: 40 Patients

Treatment

• Lithium: Best number of trials to response ratio
  • 70% complete response
  • 20% moderate response
  • For 90%, dose 300 mg at bedtime

• Caffeine
  • 28% complete response
  • 43% moderate response

• Also:
  • Indomethacin, melatonin (A few with complete-moderate response)
  • Topiramate, gabapentin, propranolol, feverfew, ibuprofen, naproxen, diazepam, feverfew, amitriptyline (all had 1-2 with moderate response)

Other Hypnic Headache Treatments

• Not tried by Tariq et al:¹
  • Acetazolamide²
  • Clonazepam³
  • Pregabalin⁴
  • OnabotulinumtoxinA⁵

• Ineffective by Tariq et al:
  • Triptans⁶

A Few Concluding Thoughts on Other Primary Headaches

• We share the same thoughts on TACs and Other Primary Headaches
• These disorders probably should be considered secondary until proven otherwise
• Cough headache, especially in the young, should make one think of posterior fossa lesions
• Sex and exercise headaches, especially in older patients, should make one think of bleed
• Thunderclap is always secondary until every rock is turned
• Hypnic headache and New Daily Persistent Headache can sometimes turn out secondary as well: think CSF, vascular, neoplastic, inflammatory, metabolic, and infectious
• The longer the attacks have been going on, the less worry
Case 3: Doing Badly

- 41 year-old female with an 11-y hx of daily headaches
- L-sided headaches, excruciatingly severe, with maximal pain retro-orbital to temple
- Occur 5-6 times/day; last 30-60 minutes untreated
- Ipsilateral ptosis, tearing, photophobia, nasal congestion
- Restless during attacks
- Constant low-level left-sided ache
- HA-free once for 10 days (while on prednisone)
• Current preventive meds: Verapamil SR 240 mg tid
• Prior rx: Verapamil SR 240 tid + VPA 1500 mg + lithium 900 mg; VPA and lithium levels in high therapeutic range
  • Topiramate at 200 mg day unhelpful
  • IV DHE for 5 days had no effect
  • Prednisone only prevents headache at 60-80 mg/day
• Medical and neurological exams are normal
What is the Diagnosis?

1- Cluster headache
2- Paroxysmal hemicrania
3- SUNCT syndrome
4- Hemicrania continua
5- Don’t know yet
What is the Diagnosis?

1-Cluster headache
2-Paroxysmal hemicrania
3- SUNCT syndrome
4-Hemicrania continua
5-Don’t know yet
ICHD-3 Cluster Headache diagnostic criteria

A. **At least 5 attacks** fulfilling criteria B-D

B. **Severe or very severe unilateral orbital**, supraorbital and/or **temporal** pain lasting **15-180 (30-60)** minutes if untreated

C. Headache is accompanied by at least one of the following:
   1. **Ipsilateral conjunctival injection and/or lacrimation**
   2. Ipsilateral nasal congestion and/or rhinorrhea
   3. Ipsilateral eyelid oedema
   4. Ipsilateral forehead and facial sweating
   5. Ipsilateral miosis and/or ptosis
   6. A sense of **restlessness** or **agitation**

D. Attacks have a frequency from **one every other day to 8/d**

E. Not attributed to another disorder

- **Episodic Cluster**: pain-free remission periods of ≥1 month/year
- **Chronic Cluster**: no pain-free period lasting ≥1 month/year

- She has had an 11 year continuous headache except when taking high-dose prednisone, she **potentially meets criteria for cluster!**
ICHDI-IIIβ
Diagnostic Criteria For Cluster Headache

A. At least five attacks fulfilling criteria B–D

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

Hers are 30-60 minutes

C. Either or both of the following:

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

2. A sense of restlessness or agitation

D. Attacks have a frequency between QOD and 8/ day for more than half of the time when the disorder is active
Cluster Headache attacks: Clinical Features

- Sex ratio (M:F): 2-6:1
- **So her gender makes cluster less likely**
- Usual age of onset late 20’s to **early 30’s**
- Attacks recur from once every other day to 8 times daily
- **Her attacks are 5-6/d, fits**
- Temporal profile: attacks recur the same time each day and night
  
  **Not described; need to go back & ask about alarm clock periodicity**

- Individual attacks are brief lasting between 15 and 180 minutes (mean 45 minutes) (**Hers are 30-60min**)
Cluster Headache: Clinical Features

• Headaches are unilateral, rare side-shift (fits)
• Maximal pain is retro- and peri-orbital (fits)
• Pain may radiate into ipsilateral temple, jaw, upper teeth and neck (fits)
• Pain is excruciatingly severe “hot poker” (fits)
• Autonomic features (ptosis, tearing, nasal congestion) (fits)
• Pacing activity (fits)
• Suicide
• ETOH trigger (go back & ask)
• Trigger with exercise or gasoline fumes or napping (go back and ask)
Cluster Headache: Clinical Features

- Episodic Cluster: pain-free remission periods of $\geq 1$ month/year
- Chronic Cluster: no pain-free period lasting $\geq 1$ month/year

She has had an 11 year continuous headache except when taking high-dose prednisone, she potentially meets criteria for cluster.
PET During Cluster: Regional cerebral blood flow Increases in Ipsilateral anterior hypothalamus

But what about…

- Her gender (~25% of CH patients)
- The persistent low level pain between the attacks (~ 1/3 of CH patients)
- The high frequency of attacks (5-6/day) (In the IHS criteria, but makes you think…)
- The unilateral photophobia (makes you think…)
- Alarm clock periodicity (We need to ask)
ICHD-3 Beta Paroxysmal Hemicrania (PH)

A. At least 20 attacks fulfilling criteria B-E
B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2–30 minutes
C. At least one of the following, ipsilateral to the pain:
   1. conjunctival injection and/or lacrimation
   2. nasal congestion and/or rhinorrhea
   3. eyelid edema
   4. forehead and facial sweating
   5. forehead and facial flushing
   6. sensation of fullness in the ear
   7. miosis and/or ptosis
D. Attacks frequency >5/day for > 50% of the time
E. Attacks prevented absolutely by therapeutic doses of indomethacin
F. Not better accounted for by another ICHD-3 diagnosis
The Paroxysmal Hemicranias: Clinical Features

• Strictly unilateral without side-shift
  • 4 reports of side-shift; 1 bilateral case
• Maximal pain is ocular, temporal, maxillary and frontal
• Excruciatingly severe; “clawlike”, aching, throbbing, boring
• Can be less severe than cluster
• Typical duration 14 minutes (up to 2 hrs)
• Interictal discomfort in 1/3 (same as cluster)
• Again, it is chronic paroxysmal hemicrania (CPH)
  if there is not 1 month off per year, F:M is 2:1
• EPH F:M is 1:1
The Paroxysmal Hemicranias: Clinical Features

- Ipsilateral cranial autonomic features \((\text{fits})\)
- Photophobia \((\text{fits})\) and nausea occasionally
- 50% lie still; \textbf{50% pace during attack}
- Attacks usually occur spontaneously
  - 7% of patients report ETOH trigger \((\text{Need to ask})\)
- Lack of alarm clock periodicity \((\text{Need to ask})\)
- There is no gender predominance \((\text{fits})\)
- Onset is usually in adulthood \((\text{fits})\)
- Unlike cluster, attacks more frequent and of shorter duration
  - 4-38 attacks daily (mean 14)
  - Attacks last 3-46 minutes (mean 14)
- \textbf{She has 5-6 attacks per day, lasting 30-60 minutes, so she mostly fits}
PH PET: Contralateral Hypothalamus and Contralateral Ventrolateral Midbrain

Right-sided Pain

No Pain

ICHD-3 Beta Hemicrania Continua

A. **Unilateral headache** fulfilling criteria B-D

B. Present >3 months, w/exacerbations of moderate/greater intensity

C. Either or both of the following:

1. ≥ one of the following **ipsilateral** to the headache:
   a) conjunctival injection and/or lacrimation
   b) nasal congestion and/or rhinorrhea
   c) eyelid edema
   d) forehead and facial sweating
   e) forehead and facial flushing
   f) sensation of fullness in the ear
   g) miosis and/or ptosis

2. Restlessness or agitation, or pain aggravation by movement

D. Responds absolutely to therapeutic doses of indomethacin

e. Not better accounted for by another ICHD-3 diagnosis.
Hemicrania Continua

- Baseline lower level hemicranial headache (she has this)
- Superimposed exacerbations of severe pain (she has this)
- Exacerbations last minutes to days; associated with ipsilateral autonomic signs (she has this) and/or migrainous features (she had photophobia)
- Stabs and jabs, foreign-body eye sensation
- Indomethacin-responsive (never tried it)
Hemicrania continua clinical pearls

• ICHD2: Continuous pain without side shift
• Often, HC complain only of the exacerbations (she did).
• Ask about the presence or absence of HA-free time!
• Additional features of HC:
  • Foreign body sensation in the ipsilateral eye or itchy eye
  • Ice pick pains/primary stabbing HAs, indomethacin-responsive
  • Ice pick pains occur in 40% of migraineurs, but are a useful addition to the HC-associated features (Not asked)
• Daily HA can be mild (IHCD-2 says moderate) (hers were)
• Exacerbations in HC often respond to triptans (Need to find out)
• Indomethacin trial often only way to distinguish CM/MOH and HC w/migraine sx
• Cittadini & Goadsby. Brain. 2010;133(Pt 7):1973-86:
  • Ipsilateral photophobia (she has it)
  • Agitation or verbally abusive during exacerbations (agitation)
  • Baseline pain 6/10 with severe exacerbations
  • Often require high doses of indomethacin (1/3 300 mg)
HC: PET shows the opposite of CH and Migraine: Contralateral Hypothalamus and Ipsilateral Midbrain.

Matharu et al. *Headache* 2004;44:747-761
So, What’s the Diagnosis?

• 1-Cluster
• 2-Paroxysmal hemicrania
• 3-Hemicrania continua
• 4-Don’t know yet
So, What’s the Diagnosis?

• 1-Cluster
• 2-Paroxysmal hemicrania
• 3-Hemicrania continua
• 4-Don’t know yet
What do we need?

• Past work-up
  • MRI with and without contrast-normal
  1-MRI brain with contrast
  2-MRA brain
  3-CT brain with contrast
  4- EEG
  5-No further work-up required
What do we need?

1-MRI brain with contrast
2-MRA brain
3-CT brain with contrast
4- EEG
5-\textbf{No further work-up required}
So, What’s the Diagnosis?

1-Cluster
2-Paroxysmal hemicrania
3-Hemicrania continua
4-Don’t know yet
Chronic Cluster

In favor
• Duration
• Severity
• Location of pain
• Autonomic features
• Restless during attacks
• Lack of remissions
• Acute treatment response

Against
• Gender
• Ipsilateral photophobia
• Low level headache interictally
• No alarm clock timing
• Inconsistent ETOH trigger
In favor
- Gender
- Duration 30-60 min attacks
- Frequency 5-6/day
- No alarm clock periodicity
- Autonomic features

Against
- Not more than 6/d
- Duration a bit long
- Ipsilateral photophobia
- Restless (reported but less common than CH)
- Severity (more common in CH)
- Continuous low level headache
### In favor
- Continuous headache
- Cluster-like exacerbations
- Ipsilateral photophobia
- Agitation
- Severity
- Gender
- No alarm clock

### Against
- Severe attacks
- High frequency
What Would You Do Next?

1-Begin indomethacin
2-Discontinue verapamil
3-Begin prednisone
What Would You Do Next?

1-Begin indomethacin
2-Begin verapamil
3-Begin prednisone
Here’s What Dr. Newman Did

- Trial of indomethacin 25 tid for 1 week
- Gradually increased dose to 250 mg daily for 2 weeks- no benefit
- Most likely not dealing with CPH or HC
Now what? Outside the box for cluster

- Kudzu
- Ergots
- LSD & psilocybin
- 2-Bromo LSD (experimental)
- GON blocks
- SPG blocks
- GON stimulators
- SPG stimulators
- SPG ablation
Kudzu for Cluster

- N= 16 Results
- 11 (69%) experienced decreased intensity of attacks
- 9 (56%) had decreased frequency
- 5 (31%) had decreased duration
- “Minimal side effects”
- Suggested dose: 1500 mg TID

Ergots for Cluster

- No triptans with ergots, so O2 becomes the acute rx
- Methylergonovine 0.2-0.4 mg TID (active breakdown product of methysergide)
- Ergotamine each night
- Vasoconstriction and fibrotic complications
LSD, psilocybin, 2-bromo LSD

- N=53 CH patients who used psilocybin or LSD
- 22/26 users: psilocybin aborted attacks
- 25/48 psilocybin users and 7/8 LSD users reported cycle termination
- 18/19 psilocybin users and 4/5 LSD users reported remission period extension\(^1\)
- BOL-148 is a non-hallucinogenic LSD
- N= 5; one ECH in cycle; 4 CCH patients
- 3 single doses over 10 days broke the CH cycle or ↓frequency and intensity; one went from CCH to ECH; one had prolonged remission\(^2\)

Stimulators or SPG Ablation for Cluster

- **Occipital nerve stimulators** for CCH
  - N=23; responder rates 37% to 66%\(^1\) **but approval in EU rescinded due to adverse events**
- **Implanted Sphenopalatine ganglion (SPG) stimulator**
  - EU RCT published\(^2\); CE Mark granted in Europe, >400 pts implanted
  - **Registration study underway in the US currently**
- **Deep brain stimulation**
  - N=52; responder rates 50-100%
  - 1 death; 3 TIAs/strokes\(^3\)
- **Non-invasive vagal nerve stimulator** approved in Canada and EU and currently before the FDA
- **SPG RF ablation**: N= 15 CCH patients who had relief w/SPG block
  - ↓Mean attack intensity to 2.6-4.2/10 from 1-18 mos follow up
  - ↓Mean attack frequency from 17 to 5.4- 8.3 from 1-18 mos\(^4\)

Anti-CGRP or receptor Monoclonal Antibodies for Cluster Prevention

• Galcanezumab in registration studies in US for both Episodic and Chronic Cluster
• Fremanezumab and erenumumab may be studied for cluster prevention
Case 3: What worked

- Verapamil short acting 80 mg QID and increased prn
- Sumatriptan 4 or 6 mg sc
- O₂ 10 l/min prn
- Headaches remitted within 2 weeks
- Over past 2 years, lowering the dose of verapamil resulted in headache recurrence within 5 days
The myth of long acting verapamil

- Short acting verapamil $t_{1/2}$ 5–12 h
- Dosing should be at least 3 times a day for generic short acting verapamil
- Verapamil SR $t_{1/2}$ 2.8-7.4 h
- With repetitive dosing, $t_{1/2}$ 4.5- 12.0 h
- Verapamil SR and generic short acting verapamil have essentially equivalent half lives
- Both require tid dosing!

Calan SR Prescribing Information, labeling Pfizer.com, accessed 10-21-12.
Conclusions: Dx- Chronic cluster

- There is considerable overlap in the frequency and duration of attacks in the TACs\(^1\)
  - Cluster can occur more than 8 times daily
  - PH can occur less than twice daily
- Ipsilateral photo/phonophobia occur in up to 50% of cluster sufferers\(^2\)
- Migrainous features (nausea, photo/phonophobia) may occur with cluster and PH\(^3\)
- More than 30% of patients who suffer from one of the TACs report interictal pain\(^4\)
- More common in patients who have a personal or family history of migraine (also true in HC)

Case 4- 35 year old man with embarrassing new headaches

• Starts as a dull bilateral ache increasing as sexual excitement increases
• Then, sudden, severe, explosive headache at orgasm
• Has occurred 3 times in the last 3 weeks, not every time, and once with masturbation
What Further Testing Should be Done?

1- CT brain
2- MRI brain
3- MRA or CTA
4- Lumbar puncture
5- 4-vessel angiogram
6- None of the above
What Further Testing Should be Done?

1- CT brain
2- MRI brain
3- MRA or CTA
4- Lumbar puncture
5  4-vessel angiogram
6- None of the above
Workup of sex headaches

• Mandatory to evaluate the vascular system with the presentation of these headaches
• Specifically look for aneurysm, arteriovenous malformation, or dissection, and look for subarachnoid hemorrhage
• Minimal workup MRI or CT, MRA, and LP, if patient presents close to first attack
• Consideration for CTA or angiography must be given
• Other causes include CSF leaks, cervical spine lesions, and posterior fossa lesions
Sex headaches: Clinical Pearls

- Men > women (3-5:1)
- 20-50% have migraine
- 30-40% also have Primary exertional headaches
- Duration <1 minute-3 hours
- Character explosive or throbbing
- Quality severe
- Location generally global for the orgasmic type.
- **Primary** sex headaches younger patients (mean age 41)
- **Secondary** sex headaches from SAH in older patients (mean age 60)
Treatment of primary headaches associated with sexual activity

- Indomethacin 50-100 mg 30-60 minutes prior to sexual activity
- Other NSAIDs may be effective occasionally
- Naratriptan 2.5 mg prior to sexual activity
- Anecdotal descriptions for other triptans, ergots, and benzodiazepines
- Long-term prophylaxis include:
  - Indomethacin 25 mg tid
  - Propranolol 120-240 mg/d & metoprolol 100-200 mg/d
  - Diltiazem 180 mg/d

Turner and Harding. *Headache* 2008; 48;1254-1256.
Case 5: Constant Headache in an Adolescent Girl

- An 15 year old female presents with her parents
- She complains of a 1 year history of daily headaches
- She states that the location is “basically all over” and varies in severity
- She recalls awakening with the headache on December 14th-it has persisted since
- When severe there is associated nausea but not photo- or phonophobia
- She was referred by a local neurologist who has tried 12 different medications without benefit
- Prior doctor recommended that she see a psychiatrist
- What Do You Do Now?
ICHD-3 New Daily Persistent Headache

A. Persistent headache fulfilling criteria B and C
B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours
C. Present for <3 months
D. Not fulfilling ICHD-3 criteria for any other headache disorder
E. Not better accounted for by another ICHD-3 diagnosis.

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
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<tbody>
<tr>
<td>• Chronic Migraine</td>
<td>□ CSF Leak</td>
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<tr>
<td>• Chronic Tension-Type</td>
<td>□ IIH</td>
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<tr>
<td>• Hemicrania Continua</td>
<td>□ Neoplasms</td>
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<td>□ Vasculitis</td>
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<td>□ Infectious</td>
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<td>□ Metabolic/Endocrine</td>
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New Daily Persistent Headache (NDPH)

- NDPH has features of either chronic tension-type headache or migraine
- No prior headache history
- Identifiable time of onset
- May follow viral illness, stressful life event, head injury
- There may be two clinical subtypes: a self-limited form and a refractory persistent form (approximately 75%)
- 6/71 responded to nortriptyline; 4/77 to topiramate
- Treatment is unsatisfactory in most patients

Evans and Rozen. *Headache* 2001;41:830–832.
Case 6-White Matter Lesions on MRI

- A 39 year old women presents with bilateral, throbbing headaches associated with nausea, and photophobia.
- In the past headaches occurred 3 times monthly, responded to treatment with NSAIDs.
- Over the last several months she reports right arm numbness accompanying some of her headaches as well as increasing frequency of headaches.
- The patient’s medical and neurological examinations are normal.
- Her maternal grandmother suffered from migraine without aura.
- Because of these new symptoms you order an MRI of the brain which reveals scattered white matter hyperintensities on T2. The radiologist report states that demyelinating disease must be excluded.

What do you do now?
White Matter Lesions on MRI
What Do You Do Now?

1. Repeat MRI with contrast
2. Repeat MRI in 6 months
3. Lumbar puncture for OCB
4. None of the above
Causes of WMH and Headache

- Migraine with and without aura
- Mitochondrial encephalopathy with lactic acidosis (MELAS)
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- CNS vasculitis
- Systemic vasculitides that involve cerebral arteries
- Anticardiolipin antibody syndrome
- Multiple sclerosis (MS)
WMH Differences

- MELAS
  - Predilection for the occipital and temporal lobes
  - Involve both the gray and white matter

- Vasculitis
  - Effect gray and white matter
  - Contrast – enhancing
Multiple Sclerosis

- Resemble those seen in migraine but unlike migraine:
- Involve the corpus callosum, cerebellum, and brainstem.
- Ovoid-shaped lesions that align perpendicularly to the ventricles ("Dawson’s fingers")
Symmetrical and confluent, best visualized on T2 and FLAIR sequences

Most prominent in the frontal and anterior temporal lobes

Associated with diffuse lacunar-type infarcts in the deep white matter and basal ganglia
White Matter Abnormalities in Migraine

- Are 4 times more likely than in non-migraineurs, particularly in women
- Small, punctuate lesions, affecting deep white matter
- Best seen on T2 and FLAIR sequences
- More common in frontal subcortical regions and centrum semiovale before age 40
- Lesions in deeper white matter, basal ganglia after age 40

Case 7: A 34 Year Old Woman Presents For The First Time

- 6-year history of recurrent bouts of left-sided headaches
- Cycles occur twice yearly and last 8-10 weeks each
- Attacks are excruciatingly severe retro-orbital and temporal, radiate into upper teeth
- Attacks recur 5 times daily; last 15-45 minutes each
- Left-sided conjunctival injection, lacrimation, photophobia
- Restless during attacks
- Constant low-level ache between attacks
- Normal medical and neurological exams
What is the Diagnosis?

• 1-Cluster headache
• 2-Paroxysmal hemicrania
• 3- SUNCT syndrome
• 4-Hemicrania continua
• 5-Don’t know yet
What is the Diagnosis?

1- Cluster headache
2- Paroxysmal hemicrania
3- SUNCT syndrome
4- Hemicrania continua
5- Don’t know yet
Additional Teaching

• Let’s say we know this patient may have cluster or PH
• What else can we teach?
More on Cluster Headache - Epidemiology

- Rare disorder affecting approximately 0.5% of the US population
- M:F 3-4:1
- Age of onset ranges from childhood to 7th decade
- Usual age of onset late 20’s to early 30’s
- May have a familial predisposition
  - 14-fold risk of cluster among 1st degree relatives
  - 17% had 1st degree relative with cluster (fathers 6%; mothers 3%)
  - 52% had family history of migraine

More on Cluster Diagnosis

• Initial diagnosis made by:
  • GP-34%
  • Neurologist (non-HA specialist)-52%
  • Neurologist (HA specialist)- 22%

• Time delay to diagnosis:
  • < 1 year-25%
  • > 5 years-42%
  • > 10 years-22%

• Correct initial diagnosis in only 21%

Cluster Headache: Clinical Features

- Pain is excruciatingly severe “hot poker”
- Suicide:
  - Ideation 55%
  - Attempts 2%
- Triggers: alcohol, nitroglycerine, weather changes, odors, bright/flashing lights, watching TV

Cluster Headache: Acute Treatment Options

- Sumatriptan 4-6 mg. sc at headache onset*
- DHE-45 0.5-1.0 mg SC, IM, IV*
- 100% oxygen inhalation at 8-10 liters/min.
- Ergotamine tartrate SL, PO
- Lidocaine 4-6% nasal drops at headache onset and 14 mins. later
- Zolmitriptan NS 5mg
- DHE NS
- Sumatriptan Breath-powered Dry Nasal powder, 11-22 mg
- FDA Approved

Cluster Headache: Bridge or Transitional Therapies

- Corticosteroids—prednisone 60-80 mg/day tapered over 10-21 days
- Ergotamine—1-2 mg PO BID-TID
- DHE—0.5-1 mg IV q 8 h for 3-5 days, or 1 mg IM 1-2 times daily for 1 week
- Naratriptan—2.5 mg BID for 1 week
- Occipital nerve blocks
- Melatonin
- No agents are FDA approved
Cluster Headache: Prophylactic Therapies

- Verapamil 120-720 mg/day in divided doses
- Methysergide 2-8 mg/day Methylergonovine 202-0.4 mg up to QID
- Ergotamine tartrate up to 4 mg/day
  - Suppositories at bedtime to prevent nocturnal attacks
- Lithium carbonate 300-1200 mg/day
- Sodium valproate 250-2500 mg/day
- Topiramate 50-200 mg/day
- Indomethacin 75-250 mg/day
- Melatonin 3-10 mg HS
- No agents are FDA approved
What about PH?
Secondary Causes of the Paroxysmal Hemicranias

• **Vascular:**
  • Aneurysms, AVM, stroke, collagen vascular dz

• **Tumors:**
  • Frontal, sella, cavernous sinus, pituitary, metastases, Pancoast

• **Other:**
  • Maxillary cyst, intracranial hypertension, essential thrombocytthemia
Paroxysmal Hemicranias: Work-up and Treatment

- MRI scan in all patients
- Indomethacin 25 mg tid (Not FDA Approved)
  - No response or partial response after 5 days—increase to 50 mg tid for 10 days
  - If high index of suspicion increase to 75 tid for 10 days
  - Initial dose of 150 mg/day up to 225 mg/day (ICHD-IIIβ)
- Complete resolution is prompt, within 1-2 days of effective dose
- GI protection
- Continue slightly longer than usual cycle (EPH)
- Try stopping every 6 months in CPH
Paroxysmal Hemicranias: Indomethacin Non-Responders

• Reconsider diagnosis
• Need for escalating doses, or if high doses are required-look for secondary cause
• Partial effect reported with:
  • Aspirin, naproxen, piroxicam, celecoxib, verapamil, flunarazine, acetazolamide, corticosteroids
• No agents are FDA approved
What about SUNHA (Short-lasting Unilateral Neuralgiform Headaches)?

- SUNCT
- SUNA
SUNCT Syndrome
(Short-lasting Unilateral Neuralgiform headaches with Conjunctival injection and Tearing)

- Rarest of short-lasting headache syndromes only 53 reported cases
- Male predilection – 2.1:1
- Age of onset ranges from 10-77 years (mean 52)
- Brief paroxysms of pain lasting 1-600 seconds each
- Attacks recur 5-6 times per minute
- Severe stabbing pain in orbito-temporal area
- Marked ipsilateral conjunctival injection and tearing
SUNCT Syndrome: Clinical Features

- Ipsilateral conjunctival injection and lacrimation-begins 1-2 seconds after pain
- Rhinorrhea if present is delayed
- Trigger zones, no refractory period
- Neck movements may trigger attacks
- Unlike cluster, patients are not restless
SUNCT: Attack Phenotypes

Pain (Verbal Rating Scale from 0 to 10)

1. Single stabs
2. Each attack is a group of stabs
3. Saw-tooth pattern

SUNCT Syndrome: Secondary Causes

- Posterior fossa and pituitary abnormalities
  - Homolateral CP angle malformation
  - Brainstem cavernous hemangioma, HIV/AIDS, Basilar impression, craniosynostosis, ischemic brainstem infarct

- Cranial MRI
SUNCT Syndrome: Treatment

- Lamotrigine 100-300 mg./day
- Gabapentin 900-2700 mg./day
- Topiramate 50 mg./day

- No agents are FDA approved
So, Let’s Revisit This Case: What Additional Information Do We Need?

- **PMH**
  - None
- **Past work-up**
  - Sinus CT normal 5 years ago
- **Past treatments**
  - 3 rounds of antibiotics, 100 mg po sumatriptan
- **Triggers**
  - Occasionally ETOH
What Would You Do Next?

1- MRI brain with contrast
2- MRA brain
3- CT brain with contrast
4- EEG
5- No further work-up required
Here’s What Dr Newnam Did

- MRI brain with contrast
  - Normal
- MRA brain
  - Normal
- Prior history of similar attacks, normal exam and normal imaging strongly suggests a primary disorder
So, Let’s Revisit Our Case

• What is the diagnosis?

• With what should we treat her?
Now, What’s the Diagnosis?

1-Cluster
2-Paroxysmal hemicrania
3-SUNCT syndrome
4-Hemicrania continua
5-Don’t know yet
Now, What’s the Diagnosis?

1-Cluster
2-Paroxysmal hemicrania
3-SUNCT syndrome
4-Hemicrania continua
5-Don’t know yet
A 34 Year Old Woman

Gender makes us think more likely this is PH but could be cluster

- Cycles occur twice yearly : EPH vs ECH
- Attacks recur 5 times daily: EPH > 5 daily for >50% (3-30); ECH up to 8 day
- Last 15-45 mins each: EPH 2-30 mins; ECH 15-180 mins
- Left-sided conjunctival injection, lacrimation, photophobia; Restless during attacks EPH vs ECH vs HC
- Constant low-level ache between attacks: HC vs ?
What Would You Do Next??

1- Begin indomethacin
2- Begin verapamil
3- Begin verapamil and prednisone
4- Begin prednisone
What Did Dr Newman Do? Same as the other case!

- Trial of indomethacin 25 tid for 1 week
- Gradually increased dose to 250 mg daily for 2 weeks- no benefit

- Most likely not dealing with EPH or HC
Diagnosis: Episodic Cluster

• Bridge or transitional treatment with prednisone taper over 14 days
• Verapamil SR 240 mg daily in divided doses
• Sumatriptan 4 mg sc and O₂ 10 l/min prn

• As the prednisone came down, at 30 mg prednisone daily headaches recurred
What Would You Do Now?

1- Increase prednisone to 60 mg and re-taper
2- Increase verapamil to SR 240 mg bid
3- Change verapamil to lithium 300 mg bid
4- 1&2
5- Change verapamil to 80 mg tid
What Would You Do Now?

1- Increase prednisone to 60 mg and re-taper
2- Increase verapamil to SR 240 mg bid
3- Change verapamil to lithium 300 mg bid
4- 1&2
5- Change verapamil to 80 mg tid
Thank you!