Migraine
2010

Recent Advances in Neurology
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International Headache Society Classification

Primary
1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
   3.1 Cluster headache
   3.2 Paroxysmal hemicrania
   3.3 SUNCT
4. Other Headaches
   4.1 Primary Stabbing
   4.2 Cough Headache
   4.3 Exertional headache
   4.4 Sex headache
   4.5 Hyptic headache
   4.6 Primary Thunderclap Headache
   4.7 Hemicrania continua

Secondary
- infection
- hemorrhage
- trauma
- tumour
- CSF pressure change

Migraine
Age Specific Prevalence in the United States

(Lipton et al., Headache 2001; 41:646-657)

Headache

(Cephalalgia 2004;24:1-160)
Migraine
The Attacks & the Disorder

**Attacks**
- Premonitory symptoms
- Pain
  - unilateral
  - throbbing
  - movement worse
- Nausea
- Sensory sensitivity
  - photophobia
  - phonophobia
  - osmophobia
- Aura

**Disorder**
- Repeated attacks
  - < 15 days/month: Episodic
  - ≥ 15 days/month: Chronic
- Family history
- Triggers (biology)
  - Sleep: missing/excess
  - Food: skipping meals
  - Chemical: alcohol or nitroglycerin
  - Weather
  - Sensory: light, smells
  - Hormonal
  - Stress - relaxation

"The simple headaches have the same characters, and occur under the same causal conditions of heredity &c, as those in which there are additional other sensory symptoms" Gowers 1893

Migraine
Classification

- **Episodic Migraine**
- Is there Medication Overuse?
  - Analgesics ten days or more per month
- **Chronic Migraine**
  - (15+ days/month)

Migraine with aura
Migraine without aura

Migraine
a systems disorder

Migraine and the pons

Nitroglycerin-triggered
Spontaneous

Bahra et al
Lancet 2001;357:1016-1017
Afridi et al
Arch Neurol 2005;62:1270-1275

(after Goadsby et al., NEJM 2002; 346:257-270)
Brainstem activations in right and left-sided headache with PET

Left-sided headache
Right-sided headache

Afridi et al., Brain 2005; 128:932-939

Migraine - Update

- Genetics
- Pain mechanisms
- Treatment

Genetics of Migraine

Familial Hemiplegic Migraine - an ionopathy

FHMI CACNA1A: P/Q voltage-gated Ca²⁺ channel chr 19
Ophoff et al. Cell 1996; 87:53-62

FHMI ATP1A2: Na⁺/K⁺ ATPase chr 1q23
De Fusco et al. Nat Gen 2003;33:192

FHMI SCN1A: Voltage-gated Na⁺ channel chr 2
Duchgens et al. Lancet 2006;367:371

van den Maagdenberg et al., Neuron 2004;41:701-710

Infarctions in the Migrainous Brain?

Kruit et al., Brain 2005;128:2066

Rozen Cephalalgia 2007;27:557-560
Vascular change measured with 3T MRA is unrelated to migraine headache

Migraine frequency and CVS risk in females
- Meta-analysis
- Risk adjusted for BP, age, smoking, BMI, cholesterol, family history
- Highest risk for stroke: females, migraine with aura, <45, smoke & O/C

Migraine - Update
- Genetics
- Disease mechanisms
  - Premonitory symptoms
    - The neck
    - Allodynia
- Treatment

Migraine - The Premonitory Phase

(Schoonman et al. Brain 2008;131:2192)

(Schurks et al., BMJ 2009;339:b3419)

(Giffin et al., Neurology 2003;60:935-940)
Dose-dependent dopaminergic modulation of trigeminocervical complex neurons


MMA: middle meningeal artery

\[D_1\] Dopamine  \[D_2\]  \[D_2\]  \[D_2\]  \[D_2\]

A11 Modulation of Trigeminocervical Neurons

Stimulation

Lesion

Migraine - Update

- Genetics
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- Treatment

Charbit et al. J Neurosci 2009

Migraine and the Neck
Referral Pain in the Trigeminocervical Complex (TCC)

Bartsch & Goadsby
Current Pain and Headache Reports 2003;7:371-376
Migraine - Update

• Genetics
• Disease mechanisms
  – Premonitory symptoms
  – The neck
    ➢ Allodynia
• Treatment

Allodynia and migraine

• Allodynia
  – pain from non-noxious heat, cold or pressure
• Incidence
  – ...now and then extensive pain over the head may be accompanied by some general tenderness of the hairy scalp...
  – Two-thirds of 500 patients
    • Selby & Lance JNNP 1969;23:23-32
  – 71% of 44 patients
    • Burstein et al., Ann Neurol 2000;47:614
  – 63% of 16,573
    • higher for frequency & BMI
      – Bigal et al., Neurology 2008;70:1525
• Site
  – Trigeminal
  – Cervical
  – Rest of body

AwM Study

Allodynia does not predict the pain free state

- Randomised Double-Blind Placebo Controlled Parallel Group
- Allodynia surrogate: cutaneous sensitivity

Diaz-Insa et al., Cephalalgia 2009;29:119; *P = 0.031

Migraine - Update

• Genetics
• Disease mechanisms
  – Premonitory symptoms
  – The neck
    ➢ Allodynia
• Treatment
Trigeminovascular System & Migraine

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

Acute Treatment of Migraine with Sumatriptan and Naproxen

- Double-blind randomized parallel group single attack adult migraineurs

- Placebo  ■ Naproxen 500 mg  ■ SumaRT 85 mg  ■ SUMA+Npx

Study I  Study II  Meta-analysis

% patients

9  15  25  34  34  30  30
no. 190 356 361 364 382 364 362 362 362 362 799 751
pain free 2hr  pain free 2hr  Sumatriptan 100 mg

Brodos et al, JAMA 2001;287:1443
Ferrari et al, Lancet 2001;358:1668
sumatriptan

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% patients

8  10  16  25  25  14  14  23  7  14  10  23  9
no. 360 366 361 364 362 364 362 362 362 799 751
Sustained pain free  Sustained pain free  Sumatriptan 100 mg

Brodos et al, JAMA 2001;287:1443
Ferrari et al, Lancet 2001;358:1668
sumatriptan

AEs
- Nausea
- Somnolence
- Dizziness
- Paresthesia
- Dyspepsia
**Transdermal sumatriptan for migraine**

- Randomised double-blind placebo controlled study
- Subjects: migraine with & without aura
- Primary endpoint: 2 hr pain free

![Graph showing pain relief comparison between placebo and sumatriptan-td.](Goldstein et al., Cephalalgia 2009;29:10- IHC2009)

**Needle-free sumatriptan injection**

- Needle-free injection: powered by N₂
- Bioequivalent, when injected onto abdomen/thigh not arm
- Delivers: sumatriptan 6mg s.c not IMI

![Diagram illustrating injection process.](Brandes et al., Headache 2009;49:1435)

**Ergot Alkaloid (tetracyclic ergolene) Family Tree**

![Chemical structures of ergot alkaloids.](Ergotamine - Eletriptan - LY334370)

**Dihydroergotamine by inhalation (MAP0004) in the treatment of acute migraine**

- Randomised double-blind placebo controlled study
- Primary endpoint: 2 hr pain relief

![Graph showing pain relief comparison between placebo and DHE-0.5mg.](Silberstein et al., Cephalalgia 2009;29-IHC2009)

<table>
<thead>
<tr>
<th>AE</th>
<th>Placebo</th>
<th>DHE-0.5mg (actual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Cough</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Tach</td>
<td>1.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>
**Ergot Alkaloid (tetracyclic ergolene) Family Tree**

- Ergotamine
- Lysergic acid
- Lysergic acid amide
- Dihydroergotamine
- Sumatriptan
- Rizatriptan
- Floxuridine
- Methysergide

**Botulinum Toxin and Headache**

- **Chronic tension-type headache**
  - No difference in frequency; n = 300
    - Silberstein et al., Cephalalgia 2006;26:717
- **Migraine (episodic)**
  - No differences; n = 232
    - Saper et al., J Neurol 2005; 252: II 58
  - No differences; n = 495
  - Reduced frequency (?primary endpoint); n = 128
    - Chakvachang et al., Cephalalgia 2005; 25: 962
- **Chronic Daily Headache**
  - No reduction in headache frequency; n = 702
  - No reduction in headache free days; n = 355
    - Mathew et al., Headache 2005; 45: 293-307
- **Chronic Migraine**
  - Reduced headache frequency on no other preventive (sub-group *)
    - Dodick et al., Headache 2005; 45: 315
  - Two RCTs Positive for reduction in headache days (IHC 2009)

**COL-144, 5-HT1F receptor agonist, in the acute treatment of migraine**

- Randomised, single-blind placebo-controlled adaptive design
- Specific agonist: 500 fold less affinity at 5-HT1B/1D than 5-HT1F receptors
- No detectable 5-HT1B receptor agonist activity in vivo, eg., rabbit saphenous vein

**Botulinum Toxin A (Botox-A) in the preventive management of chronic migraine... in context**

- 18-65 yrs, baseline one month/ 50% days migraine/probable migraine
- Primary endpoint: headache episodes baseline vs last four weeks (20-24)
- Result: I: NS, II: significant; I/II Headache days/migraine days- significant

**Reduction in migraine headache episodes**

<table>
<thead>
<tr>
<th>Baseline, n</th>
<th>Placebo</th>
<th>Botox-A</th>
<th>Topiramate</th>
</tr>
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<tbody>
<tr>
<td>12.7</td>
<td>338</td>
<td>341</td>
<td><strong>358</strong></td>
</tr>
<tr>
<td>11.5</td>
<td>358</td>
<td>347</td>
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- Placebo: 358 (347), Botox-A: 358 (347), Topiramate: 347 (358)

**Headache episode- Four hours headache bounded by no pain; * P = 0.002; ** P = 0.001; †P = 0.01**

Bouchelet et al., Br J Pharmacol 2000;129:501
Reuter et al., Cephalalgia 2009;29:122
Botulinum Toxin A (Botox-A) in the preventive management of chronic migraine
50% responder rates

(Cephalalgia 2009;29 * P < 0.05; IHC 2009)

Trigeminovascular System & Migraine

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

Trigeminal Activation & CGRP

Ann Neurol 1988;23:193
Neuropeptides 1990;16:69

Calcitonin Gene-Related Peptide (CGRP) and Migraine

1 Goadsby et al., Ann Neurol 1990;28:183
2 Olesen et al NEJM 2004;350:1104

• CGRP is released in the cranial circulation in migraine
• BIBN4096BS (olcegepant), a CGRP receptor antagonist, is effective in migraine

• BIBN4096BS

CGRP Substance P
control
MW A
MW OA

Cat Human
Trigeminal ganglion
Superior Sagittal Sinus

( repression

Arrows

Ann Neurol 1998;23:193
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• BIBN4096BS
Calcitonin/Calcitonin gene-related peptide (CGRP) Receptor Family

• Calcitonin receptor-like receptor (CLR)
  - CGRP binds to CLR when it is co-expressed with receptor activity modifying protein 1 (RAMP1);
  - Adrenomedullin (AM) binds to CLR when RAMP2 or RAMP3 expressed;

• Calcitonin Receptor (CTR)
  - Calcitonin (CT) binds to the CTR;
  - Amylin binds to CTR in the presence of RAMP1, RAMP2, or RAMP3.

Ramp Agonist
T telcagepant
nM
CLR
1 CGRP 0.77
2 adrenomedullin 100,000
3 adrenomedullin 29,000
CTR
1 amylin 190
23 amylin 100,000

CGRP receptor antagonist telcagepant is effective in the treatment of acute migraine

• Double-blind parallel group randomised controlled trials
• Two hour pain free

CGRP receptor antagonist telcagepant is effective in the treatment of acute migraine

• Sustained pain free (SPF) at 24 and 48 hr

CGRP receptor antagonist telcagepant is effective in the treatment of acute migraine

?Gepant-class AEs- dry mouth, fatigue

(Ho et al., Lancet 2008;372:2115)
**Periaqueductal Gray Matter (PAG)**

Ergot, Triptan, CGRP and P/Q Ca\(^{2+}\) channel actions converge

Goadsby & Knight, Cephalalgia 1997;17:143


Mean±SEM change in TNC \(\alpha\_\delta\) activity after PAG agatoxin, n=18

WDR, n=16; NS, n=2

**A neural basis for photophobia**

Posterior hypothalamus

Migraine with or without aura
- With light perception \((n = 14)\) -> photophobic
- Without light perception \((n = 6)\) -> no photophobia with headache

Noseda et al., Nat Neurosci 2010; 10Jan

**Valproate but not Gabapentin inhibits thalamic trigeminovascular transmission**

Valproate but not Gabapentin inhibits thalamic trigeminovascular transmission


Bicuculline (A)

Saclofen (B)

GABA

**Occipital nerve stimulation in chronic migraine**

ONSTIM

- Double-blind randomized parallel group sham stimulation controlled study
- Note: occipital pain, fail 2 preventives, exclude MOH

*Adverse event: lead migration in 24 %

(Saper et al., IHC 2009) *\(P = 0.032\); **\(P = 0.003\)*

<table>
<thead>
<tr>
<th>Reduction in headache days</th>
<th>NS</th>
<th>9</th>
<th>27</th>
<th>4</th>
<th>6</th>
<th>39</th>
</tr>
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<tbody>
<tr>
<td>50 % responder rate</td>
<td></td>
<td>16</td>
<td>29</td>
<td>17</td>
<td>4</td>
<td>0</td>
</tr>
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Occipital nerve stimulation in migraine & chronic migraine - PRISM

- Double-blind randomized parallel group sham stimulation controlled study
- Migraine > 6 days/month or chronic migraine (ICHD-II)
- Failed two preventives/two attack treatments

Effect of ONS on Chronic Migraine

Sham- 1us, 10Hz, <1mA, 1s on 90min off
Active- 250usec/60Hz, 0-12mA

(Lipton et al., Cephalalgia 2009;29:30- IHC2009)

Transcranial magnetic stimulation for Migraine

- Randomised double-blind placebo controlled study
- Include: 50% aura episodes, aura leads to headache 90%
- Exclude: Prolonged aura, MOH
- TMS- 0.9T for 180 µs; Sham- click and vibrate
- Primary endpoint: 2 hr pain free plus non-inferiority for nausea/photo/phono
- Blinding: Thought they got active, 67% Sham and 72% active

TMS & CSD in the rat

- TMS (rise time 170µs; 1.11-1.63 T) blocked 5 of 9 needle prick (NP) induced CSD's when pulsed 30s post-NP

(Lipton et al., submitted)

(Holland et al., Neurology 2009;72-Suppl 3:A250)