International Classification of Headache Disorders-IIIβ

I-Primary
1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
   3.1 Cluster headache
   3.2 Paroxysmal hemicrania
   3.3 SUNCT/SUNA
   3.4 Hemicrania continua
4. Other Primary Headaches
   4.1 Cough headache
   4.2 Exercise Headache
   4.3 Sexual activity headache
   4.4 Thunderclap headache
   4.5 Cold stimulus: external
   4.6 External pressure: compression/traction
   4.7 Stabbing Headache
   4.8.
   4.9 Hypnic headache
   4.10 New Daily Persistent Headache

II-Secondary
5. Trauma or injury to the head
6. Cranial or cervical vascular
7. Intracranial non-vascular
8. Substances
9. Infection
10. Homoeostasis
11. Disorder head, neck, eyes…
12. Psychiatric

III-Cranial neuralgias/facial pain
- trigeminal neuralgia
- trigeminal neuropathy
- glossopharyngeal neuralgia
- nervus intermedius neuralgia
- occipital neuralgia
- Tolosa-Hunt
- Burning Mouth Syndrome

Case 1
4.1 Cough Headache
Headache precipitated by coughing or other Valsalva (straining) manoeuvre, but not by prolonged physical exercise, in the absence of any intracranial disorder.
A. At least two headache episodes fulfilling criteria BD
B. Brought on by and occurring only in association with coughing, straining and/or other Valsalva manoeuvre
C. Sudden onset
D. Lasting between 1 second and 2 hours
E. Not better accounted for by another ICHD-3 Dx

Migraine - Update

• Clinical Aspects
• Disorder mechanisms
• Treatment

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
When does migraine begin?

Episodic Syndromes that may be migraine
- Recurrent GI disturbance
  - Cyclic vomiting
  - Abdominal migraine
- Benign paroxysmal vertigo
- Benign paroxysmal torticollis

Is Infantile Colic - Paroxysmal Fussing of Infancy\(^1\)- the start?
- Definition: crying 3 hrs/day, 3 days/wk for 3 weeks
- No evidence for gastrointestinal basis
- Study\(^2\) \((n = 154)\)
  - Prevalence of colic: 14%
  - Prevalence of migraine in mothers of children with colic (PR): 2.6 [1.2-5.5]

From the GWAS...

Transient Receptor Potential Channels
- TRPV (vanilloid)
  - Cation channel
  - Low pH (protons or acid)
  - Heat: >43°C
  - Capsaicin, endocannabinoids
- TRPA1 (ankyrin repeats)
  - Located in trigeminal ganglion
  - Colocalised with CGRP
  - Mustard oil, wasabi, cinnamon
- TRPM (melastatin)
  - \(\text{Na}^+ / \text{Ca}^{2+}\) channel
  - Cold: < 20°C
  - Menthol
**Genetics and Treatment Responses in Migraine**

- Subjects from Danish Headache Center ($n=1806$)
  - Semi-structured migraine interview
  - Blood samples
  - Twelve migraine SNPs
  - Logistics regression to look for association with drug responses

- **Outcome**
  - SNP rs2651899 in PRDM16 had OR of 2.6 for efficacy to a triptan

2. Christensen et al., J Head Pain 2014;15[Suppl 1]:M3

**Chronic Migraine**

**ICHD-I**

**ICHD-II**

A. Headache frequency $\geq 15$ days for $\geq 3$ months
B. Attacks fulfill criteria for migraine without aura
C. Not attributed to another disorder

*Cephalalgia* 1988;8 (suppl 7):1-96

**ICHD-II-R**

A. Headache frequency $\geq 15$ days for $\geq 3$ months
B. Patient with at $\geq 5$ attacks of migraine without aura (MWoA) in the past
C. On $\geq 8$ days per month for three months has
   1. typical MWoA
   2. attacks treated and relieved by triptans/ergots
D. Not attributed to another disorder, particularly no medication overuse

*(Olesen et al., Cephalalgia 2006;26:742)*
**Chronic Migraine**

**ICHD-III β**

A. Headache frequency \( \geq 15 \) days for \( \geq 3 \) months

B. Patient with at \( \geq 5 \) attacks of migraine with aura (MwA) or without aura (MwoA) in the past

C. On \( \geq 8 \) days per month for three months one of:
   1. MwoA: C. pain characteristics AND D. nausea/sensitivity
   2. MwA: typical aura (B & C)
   3. Attacks considered migraine by patient and relieved by triptans/ergots

D. Not better accounted for by another ICHD-III diagnosis

ICHDF-IIII; Cephalalgia 2013;33:629-808

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**Tension-Type Headache**

*(appendix)*

- **Episodic**
  - lasts 30 mins to 7 days
  - Two of
    - pressing/tight pain
    - mild/moderate severity
    - bilateral
    - no aggravation by activity
  - Both of
    - No nausea
    - Photophobia or phonophobia, not both

- **Chronic**
  - \( \geq 15 \) days/month
  - Two of
    - pressing/tight pain
    - mild/moderate severity
    - bilateral
    - no aggravation by activity
  - Both of
    - No vomiting
    - Only one of mild nausea, photophobia or phonophobia

ICHDF-IIII-beta Cephalalgia 2013;33:629

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**Relationship of Migraine and Tension-type headache**

**Attacks**
- throbbing
- movement worse
- associations
  - nausea
  - photophobia
- phonophobia
- Aura

- Non-throbbing
- no effect of movement
- associations
  - No nausea
  - No photophobia
- No phonophobia
  - ? aura

**Patient**
- Family history
- Triggers
  - Sleep: missing/excess
  - Eating: including alcohol
  - Weather
  - Hormonal
  - Stress- relaxation

---

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

50% & 75% responder rates

*\( P < 0.05 \)*

**n**
- Placebo
- Botox-A
- Topiramate

*Headache 2010;50:921*
- Dodick et al.
- Headache 2011;31:97
- Cephalalgia 2011;31:97
- Headache 2006;46:838

\( \ast \)
Possible Mechanism(s) of Action of Botulinum Toxin in Chronic Migraine

• Peripheral sensory effect
  – Blocks release of neurotransmitters associated with peripheral sensitization of sensory afferents, such as glutamate and CGRP
  – Reduced muscle afferent (1a) input
• Trans-cranial afferent effect
  – Inhibits transmission in sensory nerves that traverse the cranium and have collateral dural branches
• Trigeminal-autonomic reflex effect
  – Inhibition of sphenopalatine ganglion activation

Migraine - Update

• Clinical Aspects
• Disease mechanisms
  ➢ Premonitory symptoms
• Treatment

Case 2

Migraine: The Premonitory Phase

* Premonitory: somnolence-Gowers, 1883
### Dopamine, the A11 and its trigeminocervical effects

Charbit et al. J Neurosci 2009

**Baseline response**

**A11**

- Post i.v.
- Post iv
- D2 antagonist

**Percentage of baseline firing**

*Percentage of baseline firing: 0, 20, 40, 60, 80, 100, 120, 140, 160, 180*

- MMA: middle meningeal artery
- *Noxious pinch
- Innocuous brush

- *n = 14
- n = 13
- n = 12
- n = 5
- n = 5
- n = 5
- n = 5
- n = 5
- n = 5
- n = 6
- n = 6
- n = 6

**Baseline response**

- 5-40 mins post lesion A11 or control
- Lesion A11 (n = 8)
- Sham (n = 5)

### Premonitory Phase of Migraine

**H₂¹⁵O PET**

- Patients with premonitory symptoms, such as yawning and thirst, and no headache
- First premonitory scan vs baseline

**Hypothalamus**

- PAG
- Dorsal pons

**Maniyar et al. Brain 2014;137:232**

### Premonitory phase of migraine

**H₂¹⁵O PET- Nausea & Photophobia**

- Patients with GTN-triggered premonitory symptoms, such as yawning and no headache
- Comparison: Photophobia or Nausea with symptom absent during premonitory phase

**Photophobia (photic sensitivity)**

- Nausea

**Maniyar et al. Eur J Neurol 2014;11:1178**

**Maniyar et al. J Headache Pain 2014;15:84**

### Triggering migraine

- Identifying triggers is a popular subject amongst migraineurs

- Provocation in migraine with aura¹
  - Patients (n=27) reporting bright/flickering lights or exercise
  - Exercise: 4/12 triggered attack
  - Lights (VEP & stroboscope): 0/12 triggered attack

- Stress and migraine²
  - Patients (n=22) with 30 days of eDiary
  - Perceived Stress Scale
  - Reduced stress associated with migraine 6, 12 & 18 hr later with OR 1.5 to 1.9
  - Increased stress not associated with migraine

2. Lipton et al. Neurology 2014;82:1395
**Migraine - Update**

- Clinical Aspects
- Disease mechanisms
  - Premonitory symptoms
- Treatment

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

- Ergotamine
- Dihydroergotamine
- Sumatriptan
- Zolmitriptan
- Eletriptan
- Rizatriptan
- Almotriptan
- Naratriptan
- Frovatriptan
- Donitriptan
- CP122,288
- 4991W93
- Anti-PPE compounds
- 5HT1F agonists
- 5HT1D agonists
- Non-triptans

**Trigeminovascular System & Migraine**

Transdermal sumatriptan for migraine

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

% Patients

![Graph showing efficacy of transdermal sumatriptan for migraine](image)

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

(Goldstein et al., Headache 2012;52:1402)
Dihydroergotamine by inhalation (MAP0004) in the treatment of acute migraine

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>DHE- 0.5mg (actual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain response 2h</td>
<td>34.6</td>
<td>* 38.7</td>
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<tr>
<td>Sustained response 2-24h</td>
<td>19.4</td>
<td>45.7</td>
</tr>
<tr>
<td>Pain free 2h</td>
<td>28.4</td>
<td>* 23.1</td>
</tr>
<tr>
<td>Sustained pain free 2-24h</td>
<td>6.7</td>
<td>* 5.9</td>
</tr>
<tr>
<td>Pain free 2-48h</td>
<td>5.9</td>
<td>10.1</td>
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<tr>
<td>Any AE</td>
<td>5.9</td>
<td>17.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Cough</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Taste</td>
<td>1.7</td>
<td>6.4</td>
</tr>
</tbody>
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(Aurora et al., Headache 2011;51:507)

Lasmiditan, 5-HT\textsubscript{1F} receptor agonist, in acute migraine

- Double-blind parallel group randomised
- Placebo-controlled trial
- Migraine with/without aura; no preventives

<table>
<thead>
<tr>
<th>Placebo</th>
<th>50</th>
<th>100</th>
<th>200</th>
<th>400</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>61</td>
<td>79</td>
<td>81</td>
<td>68</td>
</tr>
<tr>
<td>% patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain free 2hr</td>
<td>7</td>
<td>14</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>SRR 24hr</td>
<td>11</td>
<td>21</td>
<td>30</td>
<td>27</td>
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<td>19</td>
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<td>SRR 24hr</td>
<td>11</td>
<td>21</td>
<td>30</td>
<td>27</td>
</tr>
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</table>

Farkkila et al., Lancet Neurol 2012;11:405

Trigeminovascular System & Migraine

- 5-HT\textsubscript{1D} CGRP

- Figueras et al., Brain Res 2001;909:112-120

(Goadsby et al., NEJM 2002; 346:257-270)
Trigeminal Activation &
CGRP

- Cat Human
  - Trigeminal Ganglion
  - Superior Sagittal Sinus

Monoclonal Antibodies for Migraine Prevention are Effective

- Amgen AMG 334
  - Human IgG1 receptor CLR/SAMP1
    - Phase II: episodic & chronic Migraine
- Alder Biopharmaceuticals- ALD 403
  - Humanized CGRP peptide antibody
    - Phase II: episodic migraine
- Arteaus Therapeutics/Lilly- LY295174
  - Humanized CGRP peptide antibody
    - Phase II: episodic migraine
- Labrys/Tev- LBR-101
  - Humanized CGRP peptide antibody
    - Phase II: episodic & chronic migraine

CGRP receptor antagonists are effective in the treatment of acute migraine

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

Cases

- European

1. Shi et al., Headache 2014;54:1417
2. Dodick et al., Lancet Neurol 2014;13:1100
4. Bigal et al., Cephalalgia 2014;34:968
4.8 Pain in a small area without a lesion

A. Continuous pain fulfilling B-C
B. Felt in a round or elliptical shape 1-6 cm in diameter
C. Lasting hours or days
D. Not better accounted for by another ICHD-III diagnosis

**Case**

- Female – aged 52
- History of nine focal areas on the head
- Pain: sharp, severe continuous with alodynia
- Rx: nortriptyline, pregabalin, topiramate, celecoxib and onabotulinum toxin type A – improved

**Nummural headache**

1. Cephalalgia 2013:33:629

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**Transcranial magnetic stimulation for Migraine**

- Randomised double-blind placebo controlled study
- **Include**: 30% 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

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain free 2 hr</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Sustained pain free 2-24 hr</td>
<td>16</td>
<td>29</td>
</tr>
</tbody>
</table>

(Lipton et al., Lancet Neurol 2010:9:973)
Single pulse Transcranial Magnetic Stimulation sTMS

- Transcranial magnetic stimulation first described as a method to stimulate corticospinal tracts
- Based on efforts by Marsden, Merton & Morton to unravel cortical influences on the motor reflexes

Merton et al. Lancet. 1982;2(8298):597

sTMS significantly modulates cortico-thalamic activation following CSD

CSD sensitizes the sensory thalamus

Andreou et al., JHP 2013;1:I6

Transcranial magnetic stimulation blocks CSD not TCC in rat

sTMS in the UK

Migraine days reduced with duration of treatment

Bhola et al., J Headache Pain 2014;15[Suppl 1]:M22 Plus
Transcutaneous Supraorbital Nerve Stimulation

- Randomised double-blind, placebo-controlled study, 30 day baseline/90 day treatment
- Thirty minutes stimulation (supratrochlear/supraorbital n. 60Hz/16 mA) versus sham (1Hz/1mA)
- Include: migraine with and without aura, 2+/month. Exclude: failed ≥ 3 preventives; MOH
- Primary endpoint: reduction in migraine days baseline versus month three: -30% vs +5%, p = 0.02

% Patients

![Graph showing % Patients](image1)

50% Responders

![Graph showing 50% Responders](image2)

Sham ■ Active

(Shoenen et al., Neurol 2013;80:697)

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

![Graph showing migraine days](image3)

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

- Adverse event: non-target sensory symptoms

Occipital nerve stimulation in chronic migraine- ONSTIM

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

![Graph showing ONSTIM](image4)

(Saper et al., Cephalalgia 2011;31:271)

* Adverse event: lead migration in 24%
Occipital nerve stimulation in chronic migraine
St Jude

- Double-blind randomized parallel group sham stimulation controlled study
- Chronic migraine or probable chronic migraine
- Occipital pain, failed two preventives; Successful trial ≥50% reduction in pain or paresthesia
- Results: Implanted (n = 177); Primary endpoint: Failed

<table>
<thead>
<tr>
<th>Response (50%)</th>
<th>control</th>
<th>stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 14</td>
<td>52</td>
<td>17</td>
</tr>
<tr>
<td>19</td>
<td>105</td>
<td>*</td>
</tr>
</tbody>
</table>

* Adverse event: lead migration in 14%

(Silberstein et al., Cephalalgia 2012;32:1165)

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

<table>
<thead>
<tr>
<th>Odds ratios</th>
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<tbody>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>CVS disease</td>
</tr>
<tr>
<td>MI</td>
</tr>
<tr>
<td>2.16</td>
</tr>
<tr>
<td>1.23</td>
</tr>
<tr>
<td>1.73</td>
</tr>
<tr>
<td>1.03</td>
</tr>
<tr>
<td>1.12</td>
</tr>
</tbody>
</table>

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

Does Migraine “hurt” the brain?

CAMERA-I

- Population-based, 9 year follow-up
- Ctrl 83/140 and Migraine 203/295
- Adjust: age, sex, BP, diabetes, education
- Results
  - Supratentorial:
    - Increased deep white matter hyperintensities by 0.11 [0.01-0.26] ml females with MwoA: new changes
    - Not related to BP or diabetes
  - Infratentorial: no change in hyperintensities
  - Progression unrelated to headache frequency
  - No effect of hyperintensities on cognition

CAMERA-II

- Population-based, 9 year follow-up
- Ctrl 83/140 and Migraine 203/295
- Adjust: age, sex, BP, diabetes, education
- Results
  - Supratentorial:
    - Increased deep white matter hyperintensities by 0.11 [0.01-0.26] ml females with MwoA: new changes
    - Not related to BP or diabetes
  - Infratentorial: no change in hyperintensities
  - Progression unrelated to headache frequency
  - No effect of hyperintensities on cognition

EVA Study

- French population based vascular risk study
- Patients born between 1922-32
- Interviewed/diagnosis probable migraine or non-migraine
- Cohort n = 1170/migraine (166)/+aura (24)
- Results
  - Battery of ten cognitive tests showed no difference between migraine and non-migraine
  - No effect of presence of brain changes on MRI on decline

<table>
<thead>
<tr>
<th>Length</th>
<th>Severity</th>
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<tbody>
<tr>
<td>n = 9</td>
<td>9</td>
</tr>
<tr>
<td>1.5</td>
<td>*</td>
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</tbody>
</table>

- Progression unrelated to headache frequency
- No effect of hyperintensities on cognition

(Afridi et al., Neurology 2013; in press)

Is glutamate involved in human aura?

- Randomized double-blind active control parallel group multiple attack crossover
- Migraine with prolonged aura (ICHD-I)/hemiplegic migraine
- Ketamine/placebo versus Midazolam/placebo (intranasal) (2 x 3 attacks/arm)
- Primary Endpoint: reduced length or severity of attack

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<td>n = 9</td>
</tr>
<tr>
<td>9</td>
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<tr>
<td>1.5</td>
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</table>

* P = 0.032