What about the non-migraine headaches, are they not relevant?

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Disclosures

Given lectures for Pfizer, Allergan, Merck, ATI, TEVA, Novartis

Conducted clinical trials for Electrocore, ATI, Eli–Lilly

Trustee in IHS, Director in LTB and DHC

Received research funding from University of Copenhagen, ATI, Lundbeck Foundation, The Medical Society in Copenhagen, NovoNordisk Foundation and Tryg Foundation
My headache destiny

1988 Epidemiology of headache

1992 Tension-Type Headache

2001 Establishment of Danish Headache Center

2005 Multidisciplinary treatment

2008 Medication Overuse Headache

2012 Cluster Headache

2014 IIH and animal models

2016 Master of Headache Disorders
What did these headache giants teach me?

- Listen and learn from the patients
- Identify and characterize the problem
- Make a hypothesis – prove or disprove!
- Publish positive AND negative results AND suggest solutions
THE IHS classification
11/12 subgroups are on non-migraine headaches

Part I: The primary headaches

1. Migraine
2. Tension-type headache (TTH)
3. Trigeminal autonomic cephalalgias (TACs)
4. Other primary headache disorders

Part II: The secondary headaches

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
12. Headache attributed to psychiatric disorder
Epidemiology of headache
1 year prevalence

Infrequent and Frequent Episodic Tension-Type Headache 74%

Cluster headache 0.1%

Chronic tension-type headache 3-4%

Migraine 10%

Medication Overuse Headache 1-2%

Lifting The Burden
in official relations with the World Health Organization
the Global Campaign against Headache

Country-based projects 2004-2018
Migraine including MOH is the 2nd largest cause of years lost to disability globally – in Young females and in Western Europe migraine is the 1st

MOH plays a major role for burden of migraine

Global Burden of Disease Study, Lancet Neurology 2019
TTH and Migraine in the general population

Infrequent Episodic TTH 30-45%

Frequent Episodic TTH 40%

Migraine 10-15%

Chronic Migraine 1-2%

CTTH 2%

Scher et al; Lyngberg et al 2005; Jensen et al 2010; Sahler et al 2012
TTH and Migraine in the headache center

- Frequent Episodic Migraine and Frequent episodic TTH: 70-75%
- Episodic Migraine and Chronic TTH: 10-15%
- Chronic Migraine (and TTH?): 10-15%
- Pure Migraine: 1%
- Pure TTH: 1%

References:
Migraine and TTH differs but often overlap and coexist

Tension-Type Headache

Migraine

No accompanying symptoms
No aggravation by physical activity,
Muscle pain
Analgesics

Nausea,
Vomiting,
Aggravation by physical activity,
Photophobia
Phonophobia
Triptans
CGRP abs
The future of TTH?

S. Ashina et al 2020; Fernandez-de-Las-Perias C 2013; 2015; Tornoe B 2014; BK Madsen et al 2017+ 2018,
**Headache Care: Organization of Headache Service**

**Level 3: Specialized headache centres**
- 1% of all headache patients
- Rare subtypes and difficult to treat
- Multidisciplinary treatment,
- Education; Research

**Level 2: Special Interest Headache Care**
- 5-10% of all headache patients
- Identification of cluster headache and sinister headaches
- Treatment of frequent migraine and TTH

**Level 1: General Primary Care**
- 90% of all headache patients
- Gate keepers; treatment of episodic migraine and TTH
- Identification of sinister headaches
- Long-term care after discharge from levels 2 and 3

Steiner et al JHP 2012 and 2019
In the specialized clinic? Danish Headache Center – a national tertiary referral treatment center

Diagnosis given at DHC between May 2020 and March 2021

- Episodic migraine: 24%
- Chronic migraine: 12%
- Episodic tension-type headache: 9%
- Chronic tension-type headache: 4%
- Cluster headache: 3%
- Other TACs: 3%
- Other primary headache disorders: 6%
- Post-traumatic headache (PTH): 9%
- Other secondary headache: 4%
- Trigeminal neuralgia: 1%
- Other cranial neuralgias: 3%
- Persistent idiopathic facial pain (PIFP): 2%
- Medication overuse headache (MOH): 36%
Facts about MOH

1-2% prevalence

Predominance of women

Socioeconomic cost

Psychiatric comorbidities

Low quality of life

High disability

Westergaard ML et al. Monitoring chronic headache and medication-overuse headache prevalence in Denmark. 2019.
National awareness campaign to prevent medication-overuse headache in Denmark

Louise Ninett Carlsen¹, Maria Lurenda Westergaard¹, Mette Bisgaard¹, Julie Brogaard Schytz² and Rigmor Højland Jensen¹

Prevention of MOH

MOH awareness increased by 7% from 31% to 38% among the public
CGRP-receptors are found in the dural vasculature, TG, spinal trigeminal nucleus, Adelta-fibers and intracranial vasculature.

Inhibits CGRP-release (via reduced cAMP-production)

Prolonged exposure to triptans and morphine

- Upregulation of serotonin-receptor
- Upregulation of cAMP
- Increased CGRP-expression and release

Prolonged exposure to paracetamol

- Increased events with cortical spreading depression

González-Hernández et al. 2020; Crain et al. 1998; Yue et al. 2008; Labastida-Ramirez et al. 2020; S.Ashina et al. 2019; Supornsilpchai et al. 2010; Olesen et al. 2019
Is Medication Overuse harmless?
Paracetamol use during pregnancy — a call for precautionary action

Ann Z. Bauer¹, Shanna H. Swan², David Kriebel³, Zeygan Liew⁴, Hugh S. Taylor⁵, Carl-Gustaf Bornemisza⁶, Anderson M. Andrade⁷, Jørn Olsen⁸, Rigmor H. Jensen⁹, Rod T. Mitchell¹⁰, Niels E. Skakkebaek¹¹, Bernard Jegou¹²,¹³, and David M. Kristensen¹⁴

Evidence from animal models and in vitro studies

APAP exposure → Perinatal → Juvenile → Adulthood

↓ AGD
↓ Steroidogenesis
↓ Gonocyte differentiation
↓ Germ cells
↓ DNA damage

↓ Neurotransmission
↓ Cognitive performance
↓ Olfactory discrimination
↓ Motor skills
↓ Spatial learning
↓ Locomotion

↑ Ovarian insufficiency
↑ Infertility
↑ Sexual behaviour
↑ Social behaviour
↑ Learning
↑ Memory, habituation

Potential associations suggested by human observational studies

APAP exposure in pregnancy → Perinatal → Childhood → Adolescence and adulthood

↓ AGD
↑ Genital malformations

↑ ADHD, autism, hyperactivity, behavioural difficulties
↓ IQ, language

↑ Early puberty onset

MANAGEMENT OF MOH

“When medication taken to create pain-relief becomes the cause of headache”

MOH withdrawal strategies:
- Complete stop
- Restricted intake

Prevalence:
- 1-2% of the general world population.
- 30-50% in specialized headache centres.

Disabling:
- Global Burden of Disease (GBD) report:
  - 18th among 301 acute and chronic diseases
  - Second when added to migraine

1 The International Classification of Headache Disorders, 3rd edition.
2 GBD Disease and Injury Incidence and Prevalence Collaborators, Lancet 2015 and 2016
Restricted intake vs Complete Stop?

Percentage reverted to episodic headache after 12 months:
74% in program A and 46% in program B (p=0.04)

Program B: Restricted intake acute medication (max 2 days/week)
Program A: Complete stop (in 2 months)

N=53
*p<0.05 for comparison with baseline

Carlsen et al 2018
Withdrawal therapy = removing the trigger

- 65 – 75% revert to episodic headache
- 45 – 58% reduction in headache days/month

**Reduced pain intensity**
**Reduced attack duration**
**Reduced disability**
**Improved quality of life**
**Reduced depression and anxiety**
**Reduced Costs**
Comparison of 3 Treatment Strategies for Medication Overuse Headache: A Randomized Clinical Trial

Louise Ninett Carlsen, MD; Signe Bruun Munksgaard, MD, PhD; Mia Nielsen, MD; Ida Maria Storm Engelstoft, MD; Maria Lurenda Westergaard, MD, PhD; Lars Bendtsen, DMSc; Rigmor Højland Jensen, MD, DMSc

**Reduction in headache days/month after 6 months**
- W+P: 12.3 days (95% CI 9.3 – 15.3)
- P: 9.9 days (95% CI 7.2 – 12.6)
- W: 8.5 days (95% CI 5.6 – 11.5)

**80% higher chance for episodic headache in W+P**

**30% higher chance for being cured for MOH in W+P**

**Fast reduction with W and W+P**

**CONCLUSIONS**

- Awareness
- Patient education
- Take the trigger away
- Prevention of underlying headache

*Figure 1: Proposed treatment path for patients with medication overuse headache. NSAID = non-steroidal anti-inflammatory drug. CGRP = calcitonin gene-related peptide.*
Cluster Headache
Background

- Prevalence of 1/1000
- Debut in the 3rd or 4th decade
- Male to female ratio of 2:1 – 8:1
- Generally:
  - Occurs at specific times of the year
  - Occurs at specific times of the day
- Sleep is a common trigger
- High burden – also in remission(!)
- High direct and indirect costs

Barloese et al. Sleep and chronobiology in cluster headache. Cephalalgia 2015
Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. Headache 2012;
Petersen et al, in prep
Migraine and Cluster headache differs but may overlap and coexist, especially in females.
Input-oscillator mechanisms

Russell, 1981
N=77 attacks, 24 patients
75% of CH attacks begin between 21.00 and 09.00 hours.

Of the daytime attacks, 71% occur during relaxation.

Manzoni et al, 1983
N=180 patients

Kudrow, 1987
N=404 cluster periods

Russell, 1981
Manzoni et al, 1983
Kudrow, 1987
Circadian and circannual rhythmicity in cluster headache = Chronorisk

Barloese et al 2013

Barloese et al 2018

Prominent anatomical connections of the hypothalamus (here in orange) with other brain areas

May and Burstein 2019
**Pathophysiology - peripheral**

- **KOS of nasal mucosa induces CAS but not attacks**  
  (Möller et al, 2017)

- **Activation of SPG increases rCBF**  
  (Goadsby, 1990)

- **Activation of SPG induces CAS but not attacks**  
  (Guo and Petersen et al, 2018)

- **Activation of VII decreases carotid resistance**  
  (Lambert et al, 1984)

- ** Activation of TCC by stim of dura**  
  (Kaube et al, 1993; Hoskin et al, 1999)

- **SuS activated after stimulation of dura**  
  (Knight et al, 2005)

With courtesy from Barloese after Akerman et al, Headache, 2009
Pathophysiology - central

CSF-orexin lower in CH (Barloese et al, 2015)

Chronobiological features (Barloese et al, 2018)

Endocrinological derangements (Leone et al, 1993)

Modulation of dural nociceptive input by orexins (Bartsch et al, 2004)

Activation during attacks, metabolite, morphometric changes (May et al, 1998 ...)

DBS of posterior hypothalamus is effective preventive therapy (Leone et al, 2001)

Possible gene polymorphisms* HCRT2R CLOCK (Gibson et al, 2019)

With courtesy from Barloese after Akerman et al, Headache, 2009
GWAS identified 4 independent genetic risk loci, and 3 replicated in an independent sample

OR = 0.62
OR = 1.53
OR = 1.51
OR = 1.43

Migraine Risk Variant (1 out of 37)

MERTK, expressed in brain in microglia, oligodendrocytes and astrocytes. Immune response?

FHL5 is a transcription factor for cAMP response through CREB6/CREM (Synaptic plasticity)

CGRP provokes attacks but only in active disease phases

30 days attack burden prior to provocation?
- Chronic patients developing attack: 33
- Chronic patients not developing attack: 7.5

Vollesen, Snoer et al JAMA NEUROL 2018
Baseline measurements

**Q1:** CGRP, PACAP38 and VIP higher in active disease states?

- **CGRP:** No significant difference
- **PACAP38:** No significant difference
- **VIP:** No significant difference
CGRP levels and the effect of CGRP-ab’s

The Effect of Galcanezumab in episodic CH

Table 2. Primary and Key Secondary End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N=37)</th>
<th>Galcanezumab (N=49)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least-squares mean change from baseline in weekly frequency of cluster headache attacks across wk 1–3</td>
<td>-5.2±1.3</td>
<td>-8.7±1.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Percentage of patients with a response at wk 3†</td>
<td>53</td>
<td>71</td>
<td>0.046</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SE.
† Response was defined as a reduction of at least 50% in the weekly frequency of cluster headache attacks. Patients with missing data at week 3 were considered not to have a response.

Goadsby et al NEJM 2019

2 New CGRP ab’s trials are under way
Urgent need for better treatment for CH
A disease model - Symptoms and signs of Idiopathic Intracranial Hypertension

Blurred vision
Obesity
Visual loss
Papilledema
Headache
Tinnitus
Mechanisms?

Incidence and obesity rates
Pathophysiology - A metabolic disease?

Regulation of CSF secretion and absorption?

Mollan S & Sinclair A  JNNP 2016
Damkær H 2020
Does Obesity affect ICP?

Validated a novel ICP telemetry system

This unique model will allow for investigations into the regulation of ICP and serve as a foundation for developing an IIH model

- DIO have raised ICP
- ICP positively correlates with abdominal obesity

Adapted from Eftekhari 2020 FBCNS, Westgate/Hagen et al in prep
Lessons learned

- Headache disorders are much more than migraine
- Excellent insights in general physiology
- Translational research and reverse
- Hypotheses driven research
- Organization of care is crucial
- Education is the key
- Our responsibility
The New Headache Giants - Education and Inspiration?

EHF-Congress
Florence 2018

Masters of Headache Disorders 2018

Master of Headache Disorders 2020

Masters of Headache Disorders 2022??
www.mhd.ku.dk
THANK YOU

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