Faculty Disclosures

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Dr. Charles has received consulting fees and/or honoraria from Amgen, eNeura and AGA Medical.

PETER J. GOADSBY, MD, PhD, FAHS
Dr. Goadsby has received consulting fees and/or honoraria from Pfizer, Zogenix, Neuroncorp, Impax, Dr. Reddy, Zosano and Amgen. He is on the Speaker’s Bureau of Allergan, Inc., and Pfizer, Inc. He has received other financial benefits as an expert witness for the Journal Watch Neurology (manuscript preparation), Medico (Legal advice, patient advice). Dr. Goadsby’s institution has received grants from ENeura, Amgen and Allergan, Inc.

DONNA GUTTERMAN, PHARM.D
Dr. Gutterman has received consulting fees and/or honoraria from NuPatho, Teva Pharmaceuticals, Dr. Reddy Pharmaceuticals.

Learning Objectives

At the conclusion of this talk, participants will be able to:

- Recognize that episodic and chronic migraine involve overlapping trigeminovascular mechanisms
- Know the role of allodynia and central sensitization in chronic migraine
- Explain how activation of brain regions are involved in the pathophysiology of migraine
- Identify new treatment mechanisms in migraine
FHM
CACNA1A
ATP1A2
SCN1A
FAMILIAL MIGRAINE
TREXK
CK18
SUSCEPTIBILITY LOCI
PROM16
TRPM8
LRP1
ZNF555
ADARB2
GRM7
HTR7
MEF2D
TGFBR2
PHACTR1
ASTN2

TIMELINE OF A MIGRAINE

Vascular theory of migraine- R.I.P.

1. Schoonman et al., Brain. 2006;131:2192
- Nineteen patients with spontaneous migraine
- No extracranial artery dilation during attack
- Slight intracranial artery dilation during attack
- Effective treatment with sumatriptan caused no intracranial vasoconstriction

Amin et al., Lancet Neurology 2013;12:454

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**Clinical Features of Chronic Migraine**

<table>
<thead>
<tr>
<th>Often evolves from episodic migraine</th>
<th>Has overlapping phenotypic features</th>
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<tr>
<td>Allodynia</td>
<td>May be difficult to reverse</td>
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<td>Risk factor for progression</td>
<td></td>
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<td>Persists interictally</td>
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**Overlapping Mechanisms of EM and CM**

Trigeminovascular system
- Involved in episodic and chronic migraine
- More easily activated in chronic

[Diagram of neuroanatomy]
**Migraine and the Neck: Referred pain in the TCC**

- dura mater
- V ganglion
- Trigeminal nucleus
- Cervical input
- Trigemino-Cervical Complex

**Thalamic Sensitization in Migraine with Extended Allodynia**

- dura mater
- V ganglion
- First-order neuron
- Second-order neuron
- Third-order neuron
- Ipsilateral
- Contralateral
- Sensory Cortex
Cutaneous Alloodynia in Episodic and Chronic Migraine

- Non-nociceptive stimuli are painful
  - Region of spontaneous pain: sensitization of V1 neurons
  - Expanded regions: trigeminocervical complex
  - Contralateral and ipsilateral: sensitization of thalamic neurons
- Presumed mechanism of allodynia is sensitization
- Allodynia is more common in CM than EM

Pathophysiology ARS Question 1

The transition from episodic to CM involves which of the following?

a) central sensitization
b) abnormal pain modulation by brainstem nuclei
c) white matter lesions
d) large patent foramen ovale (PFO)
e) frequent use of over the counter NSAIDs

A. All the above
B. a and b only
C. c and d only
D. e only
E. none of the above

Role of the Brainstem

May play a key role in development of chronic migraine

- Neurotransmitters are similar in CM and EM
- Iron deposition in PAG related to frequency of attacks
- Pontine lesions cause CM-like headache
ACTIVATION OF BRAINSTEM DURING ACUTE MIGRAINE ATTACKS

Periaqueductal Gray Matter (PAG)
Opioids, Ergots, Triptan, CGRP and P/Q Ca²⁺ channel actions converge

CORTICAL "WAVES" IN MIGRAINE WITH AURA
Activation of Hypothalamus in Migraine

IN PREMONITORY PHASE

(Denuelle et al., Headache 2007:47:1418)

DURING AND AFTER HEADACHE

(Maniyar et al., Brain 2014:137:232)

Areas of Reduced Brain Volume in Chronic Migraine

(Valerio W et al., Headache.2008:48:110)

Grey Matter Reduction in Chronic Post-Traumatic Headache

(Rocca MA et al., Stroke.2006;37:1755)

Grey matter reduction at three months in patients with post-traumatic headache that has recovered at one year

(Obermann et al., Neurology 2009: 73:078)
MRI Lesions in Migraine

- CAMERA-2 FOLLOW-UP
  - 8.5 (7.9-9.2) years
  - Controls (n=83/140)
  - Migraine with Aura (114/162)
  - Migraine without Aura (89/134)
  - Slight increased risk of progression of deep white matter lesions in women only with migraine without aura
  - No increase in progression of brainstem hyperintensities in patients with migraine compared with controls

Palm-Meinders et al., JAMA. 2012;308:1889
CGRP (Calcitonin Gene Related Peptide) IN MIGRAINE

- CGRP is elevated in the cranial circulation in severe, acute migraine
- CGRP infusion triggers migraine
- CGRP receptor antagonists abort acute migraine
- CGRP levels are elevated in chronic migraine

2. Lassen et al., Cephalalgia, 2002;22:54

Biologic Approaches to Migraine Prevention

- Amgen ABM 334:
  - Human monoclonal IgG1 receptor CLR/RAMP1
  - Phase II: episodic & chronic migraine
- AbbVie Pharmaceuticals/ALO 499:
  - Humanized CGRP peptide antibody
  - Phase II: episodic migraine
- Arthena Therapeutics Inc. LY2951742:
  - Humanized CGRP peptide antibody
  - Phase II: episodic migraine
- Labrys/Teva LBR-101:
  - Humanized CGRP peptide antibody
  - Phase II: episodic & chronic migraine

1. Shi et al., Headache 2014;54:1477
2. Dodick et al., Lancet Neurol 2014;13 in press
4. Garone et al., Cephalalgia 2013;33:368

Summary

Although there is much to still address regarding migraine mechanisms and the brain, selected studies suggest:
- Migraine mechanisms involve the trigeminovascular system which can be sensitized
- Brainstem activation is involved in the mechanisms of episodic and chronic migraine
- Chronic migraine can produce structural brain changes over time that may be reversible
- Calcitonin gene-related peptide (CGRP) mechanisms are promising targets for anti-migraine therapeutics