UPDATE ON MIGRAINE EPIDEMIOLOGY, GENETICS, AND BASIC MECHANISMS

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DISCLOSURES
- Grant Support
  - Takeda
- Consultant
  - Alder, Amgen, Biohaven, Eli Lilly, eNeura,
  - Clinic Trial Steering Committee
  - St. Jude

EPIDEMIOLOGY
Meta-analyses indicate that migraine with aura is associated with approximately 2-fold relative risk of ischemic stroke, although significant variability between studies.

High frequency of attacks and recent onset of migraine may be associated with increased risk.

Migraine associated with 1.5 fold risk of intracranial hemorrhage (both intracerebral and subarachnoid).
Migraine with aura associated with higher risk of peri-operative stroke

Prospective hospital registry study
124,558 patients
Primary outcome ischemic stroke with 30 days of surgery
Stroke risk
Overall – 2.4/1000 patients
Migraine without aura – 3.9/1000 patients
Migraine with aura – 6.3/1000 patients

PFO and Migraine

PFO-Migraine Odds Ratios
Migraine with aura: 3.4
(p<.00001)
Migraine with or without aura: 2.5
(p=.0001)
Migraine without aura: 1.3
(no statistical significance)

Other Migraine Associations
- Parkinson’s disease

- restless legs syndrome

- Extracranial artery dissection (MCA)

- Depression
Migraine Genetics

- Familial Hemiplegic Migraine
  - FHM1: CACNA1A – P/Q type calcium channel
  - FHM2: ATP1A2 – Na+/K+ ATPase
  - FHM3: CACNA1A – Voltage gated sodium channel
  - PRRT2: Proline-rich transmembrane protein 2

- Monogenic vasculopathies with migraine as part of phenotype
  - Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) – Notch 3 Gene
  - Retinal vasculopathy with cerebral leukodystrophy (RCVL) – TREX1 gene
  - Hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy (HIMART) – COL4A1 gene

- Families with identified single gene mutations
  - CAKAL1: K+ channel
  - CTNNT2: Casein kinase 1 delta – Kinase associated with advanced sleep phase syndrome

- Gene polymorphisms associated with either increased or decreased risk of migraine based on population (GWAS) studies

KEY POINTS
- Migraines share risk loci detected by GWAS all have small effect sizes, but this does not mean that they are unimportant.
- Earlier findings from candidate gene association studies in migraine could not be replicated in a much larger GWAS dataset.
- Polygenic risk score analysis of GWAS datasets indicates genetic overlap between migraine and ischemic stroke and migraine and CAD.
- Polygenic risk score analysis of GWAS datasets indicates that migraine and MS are genetically distinct disorders, and that the groups of patients with migraine and MS are more similar to NOD patients.
BASIC MECHANISMS

TIMELINE OF A MIGRAINE ATTACK

4-72 hours

<table>
<thead>
<tr>
<th>Premoritory</th>
<th>Aura</th>
<th>Headache</th>
<th>Postdrome</th>
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<tbody>
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<td>Headache</td>
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</tbody>
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Hypothalamus
Brainstem
Cortex
Thalamus
Hypothalamus
Cortex
Brainstem
Thalamus
Hypothalamus
Cortex
Brainstem
Thalamus
Hypothalamus
Cortex

Multiple genes
Environment
Hormones
Metabolism
Drugs

Diffuse neurochemical and neurophysiological alterations
Specific neurotransmitter system dysfunctions
Basic receptors

Yawning
Polyuria
Neck Pain
Fatigue
Mood change
Light sensitivity
Sound sensitivity
Visual symptoms
Sensory symptoms
Language symptoms
Cognitive symptoms
Nausea
Headache
Cutaneous allodynia

4-72 hours

4-72 hours
Premonitory Phase

PET studies show brain activation correlated with clinical Symptoms:
- Occipital cortex – Light sensitivity
- Rostral doral medulla and PAG - Nausea
- Hypothalamus - Polyuria, mood change, appetite change


The Hypothalamus as a Therapeutic Target
- Hypothalamus has neurons that respond activity to glucocorticoids
- Hypothalamic neurons release:
  - Somatostatin
  - Oxytocin
  - Orexins
  - Dopamine
  - Other substances potentially involved in migraine
HUMAN MIGRAINE TRIGGERS:

- DELAYED MIGRAINE
  - Nitroglycerin/ GTN
  - CGRP
  - PACAP
  - Sildenafil
  - Histamine
  - Dipyridamole
  - Prostaglandin I2
  - Hypoxia
- IMMEDIATE MIGRAINE
  - Prostaglandin E2
Measuring Functional Connectivity with MRI

- Based on low frequency (.1 Hz) oscillations in blood oxygen level dependent (BOLD) MRI signal
- Synchronization of these oscillations in different brain regions is interpreted as functional connectivity between those regions.
- "Resting states" refers to activity in brain regions that occurs in the absence of external stimulation
Abnormal Functional Connectivity in Migraine

- Chronic migraine associated with altered connectivity of anterior insula, amygdala, pulvinar, mediodorsal thalamus, middle temporal cortex, periaqueductal gray, and others

For excellent reviews, see:

CGRP (Calcitonin Gene Related Peptide)
IN MIGRAINE

- CGRP is released into the jugular venous system during a migraine attack
- CGRP infusion evokes migraine
- CGRP receptor antagonists effectively abort migraine attacks
- Serum CGRP levels elevated in chronic migraine

CGRP (calcitonin gene-related peptide)

What is it?

- Peptide produced in neural cells throughout the body, involved in:
  - Pain transmission
  - Vasodilation
  - Inflammation
  - Regeneration of motor neurons

CGRP and its receptor are part of the calcitonin family of peptides and receptors

- The CGRP receptor is a complex that requires both RAMP1 and CLR
- RAMP1 and CLR are also components of other calcitonin receptors
- Ligands cross-interact with other receptors in the family
- Only the CGRP receptor has been implicated in migraine pathophysiology

ADM, adrenomedullin; AMY, amylin; CLR, calcitonin receptor-like receptor; CTR, calcitonin receptor; RAMP, receptor activity-modifying protein.


<table>
<thead>
<tr>
<th>Ligand</th>
<th>CGRP</th>
<th>Adrenomedullin</th>
<th>Amylin</th>
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<tbody>
<tr>
<td>Receptor composition</td>
<td>CLR+ RAMP1</td>
<td>CLR+ RAMP2</td>
<td>CLR+ RAMP3</td>
</tr>
<tr>
<td>Receptor isoform</td>
<td>CGRP</td>
<td>ADM1</td>
<td>ADM2</td>
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CGRP Release in Migraine Attacks

- CGRP but not neuropeptide Y, VIP, or substance P released in migraine with and without aura
- Elevated CGRP levels observed in jugular but not antecubital venous blood on same side as pain
- Greater elevation in CGRP observed in migraine with aura
- CGRP levels normalize upon treatment with sumatriptan


**Brief Communication**

Pituitary adenylate cyclase activating polypeptide and migraine

Alexandro S. Iggo, Paul Edvinsson, and Peter J. Goadsby

*Clinical and Translational Neurology*
PACAP (Pituitary adenylate cyclase activating peptide): Another Potential Therapeutic Target

- Infusion of PACAP triggers migraine in susceptible individuals
- PACAP levels elevated in circulation in migraine and cluster headache attacks
- Co-localized with CGRP in many anatomical regions
- Shares an accessory protein with CGRP (Ramp-1)
- May work synergistically with CGRP or possibly with distinct sites of action???

What Do Clinical Trials of Therapies Tell Us?

- Exciting Results with Antibodies
  - Rapid onset of therapeutic effect (within days)
  - Sustained duration of therapeutic effect – (3-12 months)
  - “Super responders” – significant subset of patients with 75% reduction in migraine days and small subset with 100% reduction in migraine days
Conclusions from Data

- Specificity of antibodies to targets definitively proves primary role for CGRP and CGRP receptor in migraine
- Efficacy of antibodies, which presumably do not cross blood brain barrier, indicates mechanism of action that is either peripheral, or in brain regions outside of BBB

Lasmiditan

- 5HT 1F receptor agonist
- Receptors are not located on blood vessels
- Does not cause vasoconstriction in animal models
- Reported efficacy as an acute therapy in migraine confirms that vasoconstriction is not mechanism of action of acute migraine therapies
- Side effect profile indicates central nervous system effects – Central site of therapeutic action

Conclusions

- Migraine is one of the leading causes of disability worldwide, and overlaps with other major causes of disability
- Advances in the understanding of migraine pathophysiology are leading to therapies that can be targeted to specific mechanisms in individual patients
- The effects of specific therapies provides important new insights into fundamental migraine mechanisms