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
Migraine and Stroke

- 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 a 1.5 fold risk of intracranial hemorrhage (both intracerebral and subarachnoid).

Migraine and Right-to-left Shunt

- Migraine with aura associated with patent foramen ovale.
- Migraine with aura associated with pulmonary right to left shunt in hereditary hemorrhagic telangiectasia.
- Multiple negative studies of PFO closure for migraine with and without aura.
Other Migraine Associations

- **Parkinson’s disease**

- **Restless legs syndrome**

- **Extracranial artery dissection (MO)**

- **Depression**

**Migraine Genetics**
# Migraine Genetics

## Familial Hemiplegic Migraine
- **FHM1** - Mutations in CACNA1A - gene encoding p/q type calcium channel (involved in neurotransmitter release)
- **FHM2** - Mutations in ATP1A2 - gene encoding Na+/K+ pump (ATPase) that controls levels of extracellular K+
- **FHM3** - Mutations in SCN1A - gene encoding neuronal Na+ channel
- **FHM4** - Mutations in gene encoding PRRT2 — gene associated with PKD and infantile seizures

## Familial Migraine (genes identified in isolated families)
- **TRESK** - Potassium channel — single family
- **Casein Kinase 1 delta** - Enzyme that phosphorylates multiple proteins including "clock" proteins in hypothalamus. Also causes advanced sleep phase syndrome — reported in 2 families by may be more common.

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

## Monogenetic 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 (COL4A1 gene)
Monogenetic 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 (RCVL) – CQ14A1 gene
Ray BS, Han BS, Han BS. Experimental studies in headache: Pain-sensitive structures of the head and their significance in disease. Arch Neurol Psychiatry 1940; 41:813-856.

Dural and cutaneous pain-sensitive structures in humans: new inputs from awake craniotomies.
DILATION OF BLOOD VESSELS IS NEITHER NECESSARY NOR SUFFICIENT FOR CAUSING MIGRAINE PAIN

- Cerebral and meningeal blood vessels are not dilated during spontaneous migraine or migraine induced by:
  - Nitroglycerin
  - Sildenafil

Schoonman GG, et al., Migraine headache is not associated with cerebral or meningeal vasodilatation—-a 3T magnetic resonance angiography study. Brain. 2008;131:2192-2200.


Some drugs that induce significant cerebral vasodilation do not cause migraine
- Vasoactive intestinal peptide

19 patients with spontaneous migraine
- No extracranial artery dilation during attack
- Slight intracranial artery dilation during attack
- Effective treatment with sumatriptan caused no intracranial vasoconstriction

TIMELINE OF A MIGRAINE ATTACK
4-72 hours

Premonitory | Aura | Headache | Postdrome

Symptoms:
- Headache
- Cutaneous allodynia

Areas:
- Thalamus
- Hypothalamus
- Brainstem
- Cortex
Premonitory Phase

PET studies show brain activation correlated with clinical symptoms:

- Occipital cortex – Light sensitivity
- Rostral dorsal medulla and PAG - Nausea
- Hypothalamus - Polyuria, mood change, appetite change

Olesen, et al. 1981
Hadjikhani et al., 2001
Cao et al., 1999
Bereczki et al., 2008
Denuelle et al., 2008

Before sumatriptan
2 to 4 h after the attack onset

After sumatriptan
4 to 6 h after the attack onset

...AND MIGRAINE WITH AURA

Woods et al., 1994
Chaloupka, 2008

...AND MIGRAINE WITHOUT AURA

Omenet et al., 2008
ACTIVATION OF BRAINSTEM DURING ACUTE MIGRAINE ATTACKS

Alterations in function and sensitization of the thalamus play a role in migraine.

AURA LANGUAGE SYMPTOMS
- Visual symptoms
- Sensory symptoms
- Language symptoms
- Cognitive dysfunction
- Fatigue
- Mood change
- Nausea
- Vomiting
- Light, sound, smell sensitivity
- Headache
- Yawning
- Polyuria
- Dizziness
- Vertigo
- Other symptoms

Migraine: a brain state
Migraine Biomarkers?

- Elevated CSF levels of:
  - Glutamate
  - CGRP
  - NFG
- Elevated blood levels of:
  - Glutamate
  - CGRP
- Decreased CSF and blood levels of:
  - Beta-endorphin


HUMAN MIGRAINE TRIGGERS:

- DELAYED MIGRAINE
  - Nitroglycerin/ GTN
  - CGRP
  - PACAP
  - Sildenafil
  - Histamine
  - Dipyridamole
  - Prostaglandin I2
  - Hypoxia
- IMMEDIATE MIGRAINE
  - Prostaglandin E2

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 receptors are present in multiple central and peripheral locations

- CGRP receptors are found in multiple areas:
  - Trigeminal ganglion
  - Dura vasculature
  - Brainstem, e.g., TNC
  - Brain, e.g., thalamus

- CGRP receptors are expressed on numerous cell types:
  - Neurons
  - Glial cells
  - Mast cells

CGRP receptors are localized at several sites within the trigeminal pathway and brain:

<table>
<thead>
<tr>
<th>Structure</th>
<th>CGRP</th>
<th>ADM1</th>
<th>ADM2</th>
<th>AMY1</th>
<th>AMY2</th>
<th>AMY3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor composition</td>
<td>CLR+</td>
<td>RAMP1</td>
<td>CLR+</td>
<td>RAMP2</td>
<td>CLR+</td>
<td>RAMP3</td>
</tr>
</tbody>
</table>

**Ligand**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>CGRP</th>
<th>Adrenomedullin</th>
<th>Amylin</th>
</tr>
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*CGRP receptor localization data are based on evidence of co-localization of the receptor components (RAMP1, CLR) and binding of CGRP receptor antagonists.*

**CGRP receptors are located on both sides of the blood-brain barrier**

- CGRP receptors may be expressed in additional brain regions in which CGRP receptor localization has not been established.

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


PACAP (Pituitary adenylate cyclase activating polypeptide) and migraine

- 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?