Pathophysiology of Migraine

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Pathophysiology of Migraine

Migraine

- Places a significant burden on the patients, their families and hence society
- Causes a great number of lost workdays
- Is often viewed as ‘not serious’ by those who do not suffer

Pathophysiology of Migraine

Migraine without aura

- Migraine without aura* =
  - common migraine =
  - ‘sick headache’
  - ‘bilious attacks’
  - 70–80% attacks

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Migraine with aura

- Migraine with aura* =
- ‘Focal’ migraine =
- Classical migraine
  - 20–30% attacks
- Migraine aura without headache
  - 1% attacks

*International Headache Society 2004 www.i-h-s.org

Pathophysiology of Migraine

Outline

- Migraine is an inherited central nervous system (CNS) disorder
- Migraineurs have hyperexcitable brains
- Migraine is progressive during an attack
  - Central sensitization

*International Headache Society 2004 www.i-h-s.org
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**The five stages of an attack**

1. **P**remonitory: Food craving, tired/yawning, heightened perception, sensitivity to light/sound, heightened sense of smell, anorexia/nausea/vomiting, malaise/lethargy, deep sleep, limited food tolerance, diuresis, poor concentration, difficulty focusing, fluid retention.

2. **A**ura: Migraine headache, visual crises, left-sided fortification spectrum, a bright stellate object appeared suddenly below and to left side of fixation (o), rapidly enlarged, first as a circular zigzag, faint on inner side, as the arc increased in size, it was broken centrally, the circular outline became oval. Rectangular lines of fortification spectrum became larger as the process extended peripherally, upper portion began to expand and lower part disappeared, phenomenon ended in a whirling focus of light 20 minutes after it began and a headache appeared on the right side.

3. **H**eadache: Migraine headache, food craving, tired/yawning, heightened perception, sensitivity to light/sound, heightened sense of smell, anorexia/nausea/vomiting, malaise/lethargy, deep sleep, limited food tolerance, diuresis, poor concentration, difficulty focusing, fluid retention.


5. **V**ery normal: Normal headache, normal.


When does a migraine start?

**The five stages of an attack: premonitory**

*Giffin N et al. Neurology 2003;60:935-40*

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**The five stages of an attack: aura**


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**Left-sided fortification spectrum**

a. A bright stellate object appeared suddenly below and to left side of fixation (o).
b. It rapidly enlarged, first as a circular zigzag, faint on inner side.
c. As the arc increased in size, it was broken centrally.
d. The circular outline became oval. Rectangular lines of fortification spectrum became larger as the process extended peripherally.
e. Spectrum extended through greater portion of the field.
f. Upper portion began to expand and lower part disappeared.
g. Phenomenon ended in a whirling focus of light 20 minutes after it began and a headache appeared on the right side.

*Dr Hubert Airy*
**Pathophysiology of Migraine**

**Vascular Theory of Migraine**
- **Aura Phase**
  - Spasm of Cerebral Arteries
- **Headache Phase**
  - Vasodilation of Cerebral Arteries

*Wolf HG. Headache and Other Head Pain. 1963.*

- Abnormalities in cerebral blood flow
  - Cerebral vasoconstriction during aura
  - Cerebral vasodilation during headache
- Inadequate to explain migraine symptoms

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**Neurovascular Theory of Migraine**
- Cortical Spreading Depression (CSD)
  - Reduction in brain electrical activity and decrease blood flow
  - Release of K+ and H+ activates sensory fibers
  - Activation of trigeminal & brain stem neurons
  - Precipitation of vasodilation


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**Migraine aura**
- Pace across the primary visual cortex is about 3mm/min
- Corresponds to the speed of cortical spreading depression

*Dr Hubert Airy*

**Pathophysiology of Migraine**

**The five stages of an attack: headache**

- **I** premonitory
- **II** aura
- **III** headache
- **IV** resolution
- **V** recovery

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Migraine Mechanisms

- H+, K+, arachidonic acid (AA) & nitric oxide (NO) released in the extracellular space of the neocortex
  - diffuse towards local blood vessels
  - depolarise perivascular trigeminal terminals
  - cause activation of the caudal portion of the brainstem trigeminal nucleus (TGN)
- At the same time, collateral axons of the activated neurons in the trigeminal ganglion (TGG) release proinflammatory peptides in meninges leading to a local inflammatory reaction
- Activated TGN produces vasodilation of meningeal vessels
  - pathway originates from the superior sagittal sinus (SSN)
  - via the spenopalatine ganglion (SPG)
  - to meningeal blood vessels
  - The perception of pain is mediated by higher-order projections from the TGN

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The five stages of an attack: resolution

- 2-12 hrs

- Premonitory
  - food craving
  - tired/yawning
  - heightened perception
  - anorexia/nausea/vomiting
  - malaise/ lethargy
  - sensitive to light/sound
  - heightened sense of smell
  - vomiting
  - deep sleep
  - limited food tolerance
  - diuresis
  - poor concentration
  - difficulty focusing
  - fluid retention
  - hangover

- Aura
  - headache
  - nausea/vomiting
  - light sensitivity
  - sound sensitivity
  - photophobia
  - phonophobia
  - diaphoresis

- Headache
  - normal

- Resolution
  - normal

- Recovery
  - normal

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The five stages of an attack: recovery

- 2-24 hrs

- Premonitory
  - food craving
  - tired/yawning
  - heightened perception
  - anorexia/nausea/vomiting
  - malaise/ lethargy
  - sensitive to light/sound
  - heightened sense of smell
  - vomiting
  - deep sleep
  - limited food tolerance
  - diuresis
  - poor concentration
  - difficulty focusing
  - fluid retention
  - hangover
  - medication

Pathophysiology of Migraine

The Genetic Basis

- P/Q type Ca++ channel
  - Presynaptic
  - Voltage gated
  - Occipital cortex
  - Trigeminal nucleus caudalis
  - Linkage to chromosome 19
- Na-K ATP Pump
  - Linkage to chromosome 1

- Activated TGN produces vasodilation of meningeal vessels
  - pathway originates from the superior sagittal sinus (SSN)
  - via the spenopalatine ganglion (SPG)
  - to meningeal blood vessels

- The perception of pain is mediated by higher-order projections from the TGN
dashed lines between TGN, SSN and regions generating the pain indicate that connections are either unknown or have not been depicted

Pathophysiology of Migraine

Hyperexcitable Cortex

- Genetic component:
  - P/Q calcium channel, Na+/K+ ATPase
  - Mitochondrial defects
- Migraineurs have a lower threshold for occipital cortex excitation than controls
- Probably due to:
  - Hyperactivity of excitatory neurotransmission
    - Na+, Ca++ channels, glutamate
    - Lower activity of inhibitory neurotransmission
    - GABA

GABA=gamma aminobutyric acid
P=0.053, Cox Regression

HA=headache.


Genetic predisposition
-- Deficient habituation during repetitive stimulation
-- Allows for surpassing or modification of threshold for migraine

External: prophylaxis, psychosocial

Internal: oestrogen, stress response, lack of food, lack of sleep

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Threshold Levels for Triggered Headaches

No Triggered HA  Triggered HA

Stimulus Intensity

Probability of Phosphene

HA=Headache.


Pathophysiology

Genetic predisposition
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External: prophylaxis, psychosocial

Internal: oestrogen, stress response, lack of food, lack of sleep

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Migraine 'Threshold'

Genetic Predisposition/Prophylaxis

HORMONAL TRIGGER

LACK OF FOOD

DEHYDRATION

MUSCULAR PAIN

LACK OF SLEEP

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Migraine 'Threshold'

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Proposed Mechanisms of Migraine Headache

Abnormal cortical activity

Hyperexcitable brain ([↑Ca++, ↑Glu, ↓Mg++])

Cortical Spreading Depression

Abnormal brain stem function

Excitation of brain stem, PAG, etc.

Activation/Sensitization of TGVS

Central Sensitization

Vasodilation

Headache Pain

Antimigraine Targets

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
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**‘Triptans’: 5HT1B/1D agonists**
- Sumatriptan
- Naratriptan
- Rizatriptan
- Zolmitriptan
- Almotriptan
- Eletriptan
- Frovatriptan

**Triptans normalize dilated arteries**

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**Recurrence with Triptans**
- Symptoms effectively treated initially
- Symptoms return
- Repeated doses needed

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**Brain Stem Involvement in Migraine**
- Brain stem aminergic nuclei can modify trigeminal pain processing
- PET demonstrates brain stem activation in spontaneous migraine attacks
- Brain stem activation persists after successful headache treatment
- Brain stem: generator or modulator?

**Pathophysiology of Migraine**

**Summary**
- Current research indicates that migraine is a familial disorder of the brain characterized by neuronal hyperexcitability and, often, central sensitization
- Migraine may be due to an imbalance in excitatory and inhibitory neurotransmission and ion channel abnormalities
- Modern acute and preventive migraine treatments, such as triptans and neuromodulators, interact with pre- and postjunctional targets; their mechanism of action may help explain pathophysiologic pathways