MIGRAINE PATHOPHYSIOLOGY

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Primary headache is a big and common problem in neurology.

The main disabling form of primary headache we've been facing with is migraine.

Headache caused by a life-threatening disorder makes only 6% out of all headaches.

The problem is: what is the possibility to recognize these 6% in the jungle of the rest 94% and how to do it?
For example: Unilateral headache with miosis
Dg: Nasopharyngeal carcinoma

Generally speaking migraine is an inherited episodic disorder of the brain involving dysfunction of subcortical structures that modulate sensory input.
Migraine: prevalence by age and gender

Introduction

Headache

History

Aim

Migraine

Genetics

Anatomy

Physiology

Pathogenesis

Summary

Migraine in the United States: a review of epidemiology and health care use.
Lipton RB, Stewart WF.
Department of Neurology, Albert Einstein Collage of Medicine, Bronx, NY.

IS HEADACHE AN EVIL SPECIFIC FOR OUR AGE?

The Migraine as a Devil's act, 19th Century - France.
In the manuscripts from the ancient town Niniva, 7th century B.C., first written notes about headache, even about the features that could resemble to a modern concept of a migraine AURA.

Also, in the manuscripts having been found out in the area of ancient Egypt - descriptions of a severe unilateral headache, the main Gods Chorus and Set had used to suffer of.
In classic stories from ancient Greece - some notes about the principal God Zeus, suffering from a very bad head pain...
...but in the new era it is much better understood than has been case for the last four millennia

Our aim here will be to explore the anatomy and physiology relevant for migraine

Un understanding of the pathophysiology of migraine will enable the clinician to give many explanations concerning this type of headache to patients

Migraine: A Common Episodic Headache Disorder

Neurologic disorder:
  • strong genetic component (up to 50%)
Migraine: A Common Episodic Headache Disorder

Global prevalence in adults: >10%
  • women: 15%–17%
  • men: 6%–9%

2 major subtypes:
  • without aura (~75%)
  • with aura (~25%)

Migraine: A Common Episodic Headache Disorder

Burden:
  • among the world’s 20 most disabling diseases (WHO)
  • indirectly costs employers up to USD 13 billion per year
  • direct medical costs exceed USD 1 billion per year
Definition of Migraine: Repeated episodes of headache (4 to 72 hours) with the following features:

Any two of:
- unilateral
- throbbing
- worsened by movement
- moderate to severe

Any one of:
- nausea/vomiting
- photophobia and phonophobia

The International Classification of Headache Disorders: 2nd edition
Headache Classification Subcommittee of the International Headache Society

One of the most important aspects of the pathophysiology of migraine is the inherited nature of the disorder.
The first report about that derives from the 17th century.
Both twin studies and population-based epidemiological surveys strongly suggest that migraine without aura is a multifactorial disorder, caused by a combination of genetic and environmental factors.

In approximately 50% of the reported families, familial hemiplegic migraine (FHM) has been assigned to chromosome 19p13.

Few clinical differences have been found between chromosome 19-linked and chromosome 19 unlinked FHM families.

The clinical phenotype does not associate particularly with the known mutations.

The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel
Faculte de Medicine, Laribosiere, Paris, France
The biological basis for the linkage to chromosome 19 is mutation, involving the Cav 2.1 (P/Q) type voltage-gated calcium channel CACNA1A gene.

Now known a FHM-I, this mutation is responsible for about 50% of identified families.

Mutations in the ATP1A2 gene have been identified to be responsible for about 20% of FHM families (FHM-II) comprising epilepsy in terms of clinical presentation.

Nomenclature of voltage-gated calcium channels
Ertel EA, Campbell II KP, Harpold MM, et al.
Department of Physiology and Biophysics, University of Washington, Seattle

Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha 2 subunit associated with familial hemiplegic migraine type 2
Human Molecular Genetics Unit, Dibit-San Raffaele, Milan, Italy
Most recently, mutations in the voltage-gated sodium channel gene SCNA1 have been identified as the cause for FHM-III.

Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine
Dichgans M, Freillinger T, Eckstein G, et al.,
Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians Universitat, Munchen, Germany

Taken together, the known mutations in familial hemiplegic migraine suggest that migraine, or at least the neurological manifestations currently called the aura, are caused by an ionopathy.
Trigeminal innervations and Pain producing Intracranial structures

- Human dural nerves that innervate the cranial vessels largely consist of small-diameter myelinated and unmyelinated fibers that almost certainly subserve a nociceptive function.

They arise from the ophthalmic division of the trigeminal ganglion and in the posterior fossa from the upper cervical dorsal roots.

- Neurons in trigeminal ganglion contain substance P and calcitonin-gene-related peptide (CGRP), both of which can be released when the trigeminal ganglion is stimulated.
Preclinical studies suggest that cortically spreading depression may be a sufficient stimulus to activate trigeminal neurons, although this is still controversial area.

Just as dihydroergotamine can block trigeminovascular nociceptive transmission, probably at least by a local effect in the trigeminocervical complex, dihydroergotamine can block central sensitization associated with dural stimulation by an inflammatory soup.
Electrical stimulation of the trigeminal ganglion in both humans and cats leads to increases in extracerebral blood flow and local release of both CGRP and substance P.

- CGRP is elevated in headache in humans.
- Also, nitric-oxide-donor-triggered migraine, also results in increase of CGRP.
- That fact is very important from the therapeutical point of view.
Data suggest convergence of cervical and ophthalmic inputs at the level of the second-order neuron (Thalamus).

Human imaging studies have confirmed activation of thalamus contralateral to pain in migrainous attack.

The role of posterior hypothalamus? Can be both pronociceptive and antinociceptive.

New therapeutic possibilities?

Functional brain imaging (PET) has demonstrated activation of dorsal midbrain as well as periaqueductal gray and in the dorsal pons, near the locus coeruleus in studies during migraine with aura.
Dysfunction of brainstem pain and vascular control centers

Brainstem activation during a spontaneous migraine attack


Dysfunction of brainstem pain and vascular control centers

Brainstem activation during a spontaneous migraine attack

Two different concepts:
• vascular concept
• neuro-vascular concept

Different forms of Migraines
• Migraine with aura
• Migraine without aura

Vascular concept
• Specific cause unknown

Key factors in migraine headache pain
• Initial intracranial vascular constriction
  - reduced blood flow triggers aura
  - intracranial extracerebral blood vessels dilate
  - activates perivascular trigeminal sensory nerves
  - initiates “pain” transmission to the brain
Vascular concept
Specific cause unknown
Key factors in migraine headache pain
- Activated nerves release neuropeptides
  - exacerbates vessel swelling - vicious cycle
  - increases pain transmission

Vascular concept
Specific cause unknown
Key factors in migraine headache pain
- Central pain transmission activates other CNS pathways
  - nausea, phonophobia, photophobia
Neuro-vascular concept

Specific cause may be related to hypersensitivity of occipital, hypothalamic and limbic cortex

Key factors in migraine headache pain

- Activation of sensory neurons, located in the trigeminal system
  - causing dilatation of the meningeal blood vessels
  - local release of neuropeptides – Substance P, nitric oxide, 5-HT, Neurokinin A and CGRP
  - plasma protein extravasation
  - initiation neurogenic inflammation
  - Initiates “pain” transmission to the brain
Key factors in migraine headache pain

- Neurogenic inflammation in the meninges causes reactive impulses
- Central pain transmission activates other CNS pathways
  - nausea, phonophobia, photophobia

THE ROLE OF 5HT

- CGRP release
- Vasodilation, inflammation
- Dilation
- Pain
1. Cortical spreading
Depression (Aura)
Vasokonstriction

2. Vasodilation
Neurogenic inflammation
Pain

3. Activation of brainstem centres

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2. Vasodilation
Neurogenic inflammation
Pain

1. Activation of brainstem centres
But...
...the fundamental problem in migraine is in the brain

MIGRAINE: INTEGRATED HYPOTHESIS

Migraine is a primary episodic headache disorder characterised by various combinations of:

- neurological
- gastrointestinal
- autonomic changes

Migraine is best understood as a primary disorder of the brain:

- genetic predisposition
- cortical, occipital, hypothalamic hypersensitivity
- temporarily disturbance of pain inhibiting systems of the brain stem (periaqueductal gray)
- release of vasoactive neuropeptides inducing neurogenic inflammation
- central sensitisation of the trigeminal system

Lancet 2004; 363:381-391
Silberstein SD.
Jefferson Headache Centre, Philadelphia, PA, USA

Migraine—current understanding and treatment
Goadsby PJ, Lipton RB, Ferrari MD.
Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, UK
The best treatment for any disease comes from understanding its pathophysiology.

- focused treatment of acute attacks
- prophylaxis

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Acute migraine: Current treatment and emerging therapies

Kalra AA, Elliot D
Department of Neurology, LSU Health Sciences Center Shreveport, LA; USA

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THANK YOU
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