40 years of human migraine research

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Migraine aura and cortical spreading depression

\( rCBF \) with Xenon\(^{133}\) and 254 channels

Speed of hypoperfusion = 2-3 mm/min

CBF changes during migraine with aura

Relative timing of CBF, Aura and Headache

- Hypoperfusion
- Hyperperfusion
- Normal CBF

Aura and Headache over time:
- Aura
- Headache

Hours after angiography

2 4 6 8 10 12
COMMON MIGRAINE DURING ATTACK

FLOW (ML/100G/MIN)
Attacks of aura

P = 0.01

Placebo

Tonabersat
Measurements during migraine attacks

Difficult to get measurements during spontaneous attacks
Patients come at different times after onset
Never at the very onset or before
Are findings cause or effect
Lots of confounding factors
Lots of false positive results
Human experimentation
Migraine without aura

GTN-induced headache intensity over time

Cumulative number of patients fulfilling the IHS criteria

Thomsen et al, Eur J Neurol 1994
NOS inhibition in Migraine
Relief 2 hours after treatment

L-NMMA
Placebo

headache
phonophobia
photophobia
nausea
disability

%
New drug targets in the NO pathway

Selective iNOS or nNOS inhibitors
Guanylate cyclase inhibitors
PDE 5 activators
Protein kinase inhibitors
Ion channel antagonists
CGRP model of migraine: migraine *without* aura

*Migraine without aura (60%)*

Lassen et al. *Cephalalgia* 2002
Regional Cerebral Blood Flow (MCA)

![Graph showing regional cerebral blood flow over time for Placebo and BIBN4096BS 2.5 mg and BIBN4096BS 10 mg.](image)

- **Baseline**
- **Time (minutes)**: 20, 40, 60, 80, 100, 120, 140, 160, 180
- **CBF**: ml \times 100 g brain tissue \times \text{min}^{-1}
- **Groups**:
  - Placebo
  - BIBN4096BS 2.5 mg
  - BIBN4096BS 10 mg
CGRP-receptor antagonist

Olesen et al. NEJM 2004
The International Classification of Headache Disorders
2nd Edition

The International Classification of Headache Disorders, 3rd edition

1988  2004  2018
Table 1. Proposed diagnostic criteria for chronic migraine (pCM).

A. Fulfills the diagnostic criteria for 1.1 migraine without aura and/or for 1.2 migraine with aura.
B. For at least 3 months, migraine headache day frequency according to criterion C has been eight or more per month.
C. Each of the migraine days fulfills at least one of the following:
   1. Criteria C and D for 1.1 Migraine without aura
   2. Criteria B and C for 1.2 Migraine with aura
   3. Believed by the patient to be migraine at onset and relieved by a triptan, an ergot derivative, a CGRP antagonist, or a 5-HT 1F agonist.
Proposed diagnostic criteria for migraine with brainstem aura

A. Attacks fulfilling criteria for 1.2 Migraine with aura and criterion B and C below.

B. Aura with both of the following by face-to-face interview by a neurologist:
   1. at least three of the following fully reversible brainstem symptoms:
      - dysarthria
      - vertigo
      - tinnitus
      - hypacusis
      - diplopia
      - ataxia not attributable to sensory deficit or weakness
      - decreased level of consciousness (GCS ≤13)
      - simultaneously bilateral visual symptoms and/or simultaneously bilateral paresthesias
   2. no motor or retinal symptoms

C. Other etiologies ruled out by examination by a neurologist, MRI and other laboratory tests. Attack related EEG abnormalities are fully reversible.

D. Not better accounted for by another ICHD diagnosis.

Yamani et al Brain 2019
Proposed diagnostic criteria for Headache Attributed to TIA

A. Headache fulfilling criterion C
B. Transient ischemic attack (TIA) has been diagnosed
C. Evidence of causation demonstrated by one of the following:
   1. Any type of headache occurring within one hour of TIA onset
   2. Any new type of headache occurring within 24 hours of TIA onset
D. Not better accounted for by another ICHD-3 diagnosis

Lebedeva E.R. et al in preparation
Conclusions

The black box containing migraine mechanisms has been opened
Many signalling mechanisms are known
Validated drug targets available for the pharma industry
Classification research needed
Revisions must be evidence based