The role of Na+/K+ ATPase in familial hemiplegic migraine and epilepsy

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Outline

- Introduction
- Familial hemiplegic migraine
  - Clinical definition
  - Etiology
  - Genetics
- Co-morbidity with epilepsy
- Na+/K ATPase
Epilepsy and migraine are common chronic disorders characterized by recurrent attacks.

- Epilepsy: prevalence of 0.5% (Hauser et al., 1991)
- Migraine: 6% of M and 15–18% of F (Lipton & Stewart, 1997)
- Several studies have reported the comorbidity of both disorders
- 6% of patients with migraine have epilepsy
- Patients with epilepsy are 2.4 times more likely to have migraine than persons without epilepsy
- The mechanism underlying both disorders may be a condition of neuronal hyperexcitability resulting from genetic or environmental factors
ON RECURRENT MOTOR PARALYSIS IN MIGRAINE,
WITH REPORT OF A FAMILY IN WHICH RECURRENT HEMIPLEGIA ACCOMPANIED THE ATTACKS.

By J. Michell Clarke, M.A., M.D. Cantab., F.R.C.P.,

The following are the points on which I base the diagnosis of migraine for the actual attacks: (1) The marked hereditary tendency, direct transmission, and absence of other neuroses in the family; (2) the onset of the affection in most of the patients in childhood; (3) the characteristic visual phenomena preceding the headache, especially temporary hemiopia; (4) headache, generally unilateral; (5) the vomiting which generally accompanied the onset of the headache, and after which the condition of the patient began to improve; (6) return to the normal in the interval between the attacks; and (7) the temporary loss of speech and sensory disturbance which are well-known features of some severe attacks of migraine. In all these points the attacks in this family
Familial hemiplegic migraine (FHM): clinical features

- Form of migraine with aura
- Clinical characteristics:
  - Aura: visual and sensory
  - Hemiplegia: transitory and fully reversible weakness of half the body on either side
  - Migraine: throbbing pain in one area of the head, often accompanied by nausea, vomiting, and extreme sensitivity to light and sound
- Duration: hours-days
- About 1 in 10,000 people
- Females > males
- Onset: 1st - 2nd decade
- Autosomal dominant inheritance
Diagnostic criteria for FHM:
1) fulfills criteria for migraine with aura
2) aura includes some degree of hemiparesis and may be prolonged
3) at least one 1\textsuperscript{st} degree relative has identical attacks
Three genes are known to be associated with FHM:

- *CACNA1A* (FHM1): 19p13
- *ATP1A2* (FHM2): 1q21-q23
- *SCN1A* (FHM3): 2q24
## Etiology

<table>
<thead>
<tr>
<th>Gene</th>
<th>% of FHM</th>
<th>Test method</th>
<th>Mutations detected</th>
<th>Co-morbidities</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CACN1A1</td>
<td>7%</td>
<td>Sequence analysis</td>
<td>Sequence variants exonic/whole gene del</td>
<td>Ataxia and cerebellar signs</td>
<td>yes</td>
</tr>
<tr>
<td>ATP1A2</td>
<td>7%</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>SCN1A</td>
<td>Rare</td>
<td>Sequence analysis</td>
<td>Sequence variants exonic/whole gene del</td>
<td></td>
<td>Yes</td>
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</tbody>
</table>
Several episodic neurological diseases, including FHM and epilepsies, are caused by mutations in genes coding for ion channels subunits, and hence classified as channelopathies.

- Migraine as a disorder of neural excitability
- Mutations in the:

  **CACNA1A** (pore-forming subunit of Ca(V)2.1)  
  gain-of-function of the Ca(V)2.1 channel, increased glutamate release at cortical synapses and facilitation of induction and propagation of cortical spreading depression (CDS)

  **ATP1A2** (alpha(2) subunit of the Na(+)/K(+) pump)  
  loss-of-function of the alpha(2) Na(+)/K(+) ATPase

  **SCN1A** (Na(V)1.1 channels)  
  accelerates recovery from fast inactivation of Na(V)1.5 channels

FHM mutations share the ability to render the brain more susceptible to CSD, by causing excessive synaptic glutamate release (FHM1) or decreased removal of K(+) and glutamate from the synaptic cleft (FHM2) or excessive extracellular K(+) (FHM3)

Further genetic heterogeneity

- Boy with HM with SLC1A3 encoding the glutamate transporter EAAT1 (Jen et al, Neurology 2005)

*PRRT2* mutations in familial infantile seizures, paroxysmal dyskinesia, and hemiplegic migraine

- Infantile convulsions and hemiplegic migraine
- Hemiplegic migraine
FHM and epilepsy: common etiology and pathways?

Genes associated with both
- SCN1A
- CACNA1A
- ATP1A2

- 60 familial & sporadic patients with FHM + epilepsy with mutations in one of the 3 genes
- About 10% of patients with FHM have epilepsy
- Usually beginning in childhood with a benign evolution
- Focal or generalized
Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new CACNA1A mutation


Neurology 2004;63(6):1136-7

Sporadic hemiplegic migraine and epilepsy associated with CACNA1A gene mutation

Zangaladze A, Asadi-Pooya AA, Ashkenazi A, Sperling MR.
Epilepsy Behav. 2010;17(2):293-5.

sporadic case of FHM1 linked to S218L CACNA1A gene mutation with hemiplegic migraine, cerebellar symptoms, and epileptic seizures
First mutation in the voltage-gated Nav1.1 subunit gene SCN1A with co-occurring familial hemiplegic migraine and epilepsy


- SCN1A mutation in a Portuguese family FHM and epilepsy partly co-segregating
- L263V mutation segregated in 5 patients, 3 had epileptic attacks, occurring independently from their hemiplegic migraine attacks
three-generation family with both epilepsy and FHM

- 5 affected individuals
  - proband had benign occipital epilepsy (BOE)
  - 2 relatives had simple febrile seizures (FS) and later developed BOE
  - 2 additional relatives had FHM without epilepsy or FS
- All affected members and 1 obliged carrier carried the T1174S mutation
- Functional effects were divergent:
  - T1174S could in some conditions induce overall *loss of function*, and in others *gain of function*
  - Modulation of the properties of T1174S lead to a switch between overall gain and loss of function, and a switch between pro-migraine and epileptogenic effect thus, with coexistence of epilepsy & FHM in the same family
Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2

De Fusco et al., Nat Genet 2003

- 1st report associating mutations of Na+/K+ pump subunits to genetic diseases

- ATP1A2 that encodes the α2 subunit of the Na+/K+ pump associated with FHM2 (OMIM 602481)

- > 50 mutations identified
  - >> missense mutations
  - Small deletions
  - Stop codon
Novel missense mutations in the ATP1A2 gene

- M731T mutation was found in a family with pure FHM
- R689Q mutation was identified in a family in which FHM and benign familial infantile convulsions partially co-segregated. In this family, all available affected family members with FHM, benign familial infantile convulsions, or both, carry the ATP1A2 mutation
Epilepsy as part of the phenotype associated with \textit{ATP1A2} mutations

*†††Liesbet Deprez, §Sarah Weckhuysen, §Katelijne Peeters, *†††Tine Deconinck, *†††Kristl G. Claes, *†††Lieve R.F. Claes, *†††Arvid Suls, *†††Tine Van Dyck, †††André Palmini, †††Gert Matthis, §Wim Van Paesschen, and *†††§Peter De Jonghe

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Proportion mutation carriers with epilepsy</th>
<th>Seizure type</th>
<th>Onset age</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Thr378Asn</td>
<td>4/4</td>
<td>Febrile and afebrile GTCS</td>
<td>18 mo-3 y</td>
<td>NS</td>
<td>Bassi et al., 2004</td>
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<tr>
<td>p.Arg689Gln</td>
<td>5/11</td>
<td>BFIS in 2</td>
<td>1.5 mo and 3 mo</td>
<td>Remission BFIS: remission; single FS</td>
<td>Terwindt et al., 1997; Vanmolkot et al., 2003</td>
</tr>
<tr>
<td>BFIS + FS in 1</td>
<td>BFIS: 3 mo; FS: 4.5 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFIS + GTCS in 1</td>
<td>BFIS: 4 mo; GTCS: 8 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.Asp718Asn</td>
<td>1/7</td>
<td>FS in 1</td>
<td>11 mo</td>
<td>Only 2x</td>
<td>Jurkat-Rott et al., 2004</td>
</tr>
<tr>
<td>p.Leu764Pro</td>
<td>3/22</td>
<td>GTCS</td>
<td>4 y</td>
<td>Treated with AEDs until 15 y</td>
<td>De Fusco et al., 2003; Marconi et al., 2003</td>
</tr>
<tr>
<td>p.Trp887Arg</td>
<td>2/7</td>
<td>PE in 1</td>
<td>6 y</td>
<td>Benign course with remission</td>
<td>De Fusco et al., 2003; Marconi et al., 2003</td>
</tr>
<tr>
<td>p.Pro979Leu</td>
<td>1/5</td>
<td>PE with secondary generalization and visual disturbances</td>
<td>NS</td>
<td>Successfully treated with AEDs</td>
<td>De Fusco et al., 2003; Marconi et al., 2003</td>
</tr>
</tbody>
</table>

10% of FHM2 have epilepsy

A novel ATP1A2 gene mutation in familial hemiplegic migraine and epilepsy

- three-generation family with 5 family members having a novel ATP1A2 mutation co-segregating in the 5 relatives with migraine, 4 of whom had hemiplegic migraine

- 3 patients presented with epilepsy, one of whom had generalized epilepsy with febrile seizures plus
10 transmembrane domains
> 50 \textit{ATP1A2}-FHM2 mutations have been reported
Na+/K ATPase pump

- Na(+)/K(+)−ATPase α2 is an integral plasma membrane protein belonging to the P-type ATPase family

- ATP1A2 contains 2 subunits, α and β, with each having various isoforms and differential tissue distribution

- Expressed in the astrocytes
Na+/K ATPase function

- Maintaining the Na+ and K+ gradients across cellular membranes with hydrolysis of ATP
  - Na in the extracellular space
  - K+ into the cell
- Coupled to various transporters
  - Glutamate transporter
  - Na+/Ca+ exchanger
- Clearance of released glutamate and K+ from the extracellular space
The role of the Na+/K ATPase in FHM

- Mutations cause a dysfunctional ion pump activity
- Functional data indicate that the putative pathogenetic mechanism is triggered by a loss of function of a single allele of ATP1A2
- Increased glutamate and K+ in the extracellular space: prolonged recovery after neuronal excitation and render the brain more susceptible to
  - Cortical spreading depression ▶️ migraine
  - Paroxysmal depolarizing shift ▶️ seizures
Animal models

- Atp1a deficient mouse: anxiety, learning disorder, fear
- Knock out and knock in heterozygous mice: increased fear, anxiety, reduced locomotor activity, increased susceptibility to CSD
Co-segregation of FHM and epilepsy

- About 10% have epilepsy
- Generalized or focal sz including: FS, GEFS+, BFIS

Mutations in genes coding for components of ion channels cause both

FHM and seizures channelopathies

Glutamate
Conclusion