Comorbidities of migraine

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• Comorbidity is greater than coincidental association of two (or more) conditions in the same individual.

  Feinstein 1963

• Migraine has been noted to be comorbid with a number of other illnesses in specialty care and in population samples.
Why is important to learn about comorbidities?

- Raise the global burden of migraine
- In clinical practice: acute and prophylactic treatment
- Insight in pathophysiology of migraine

### Conditions comorbid with migraine

<table>
<thead>
<tr>
<th>Psychiatric</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Panic disorders</td>
</tr>
<tr>
<td></td>
<td>Bipolar</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Epilepsy</td>
</tr>
<tr>
<td></td>
<td>Tourette’s*</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td></td>
<td>Stroke: ischemic, lacunar</td>
</tr>
<tr>
<td></td>
<td>Patent foramen ovale*, mitral valve prolapse*, atrial septal aneurysm*</td>
</tr>
<tr>
<td>Other</td>
<td>Snoring/sleep apnea*</td>
</tr>
<tr>
<td></td>
<td>Asthma/allergy</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus*</td>
</tr>
<tr>
<td></td>
<td>Non-cephalic pain</td>
</tr>
</tbody>
</table>

* Data from clinical samples only
• Depressive disorders are among the leading causes of disability worldwide.

• WHO estimates that major depressive disorder will become the second leading cause of disease burden by the year 2020, second only to ischemic heart disease.

Migraine and depression – bidirectional association

• Population-based cohort study
  - migraine 496
  - other headaches 151
  - control subjects 539

• Interviews in 1997, 1999
  - Major depression at baseline
    Migraine OR = 3.4 (1.4- 8.7)
    Other headaches OR = 0.6 (0.1- 4.6)

• Migraine at baseline
  Depression OR = 5.8 (2.7- 12.3)
  Other headaches at baseline
  Depression OR= 2.7 (0.9- 8.1)

*Breslau et al. 2003*
Migraine, depression and anxiety disorder

- Cross-sectional population-based study
- 64,560 participants
- Depression
  - Migraine: OR = 2.7 (2.3-3.2)
  - Non-migraine headaches: OR = 2.2 (2.0-2.5)
- Anxiety disorder
  - Migraine: OR = 3.2 (2.8-3.6)
  - Non-migraine headaches: OR = 2.7 (2.4-3.0)
- Stronger for anxiety disorder
- The ORs increased with increasing headache frequency

Zwart et al. 2003

Migraine and depression: Meta-analysis

- 47 cross-sectional and case control studies, 12 relevant
  

- The prevalence of depression
  - without migraine: 3.4 - 24.4%
  - migraine: 8.6 - 47.9%

- Overall OR 2.2 (2.0-2.3)

Antonaci et al. 2011
Migraine and other psychiatric disorders

• Anxiety disorders
  Panic attacks and phobias – increased risk
  Conflicting results: obsessive–compulsive disorder
  generalized anxiety disorder

• Other affective disorders
  Bipolar disorder – increased risk

• Substance-related disorders
  Association between migraine and drug, alcohol or
  substance abuse/dependence is not proven.


Migraine subtypes and depression

• Migraine with aura

• Chronic headache, and particularly chronic migraine, as
  compared to episodic migraine

• Suicide risk is higher:
  migraine with aura
  higher headache frequency
  females with migraine
  adolescents with chronic headaches

From children to grown-up

Anxiety → Migraine → Depression


History of abuse

- Migraineurs with current depression reported more frequent physical and sexual abuse compared to those without depression.

- Women with major depression were more likely to report sexual abuse occurring before 12 years.

- Women with migraine and depression were 4 times more likely to have a history of some type of childhood maltreatment.

Tietjen et al. 2007
Pathophysiology of the comorbidity

• At present, these mechanisms are poorly understood.

• Dopamine D2 receptor genotype and comorbid migraine with aura, major depression and generalized anxiety disorder
  
  *Peroutka et al. 1998*

• 5-HT receptors and transporters, other neurotransmitters are under investigation.

Pain conditions and psychiatric disorders

• A large sample (3032 adults), Canada

• Association between
  
  **pain conditions**: migraine, arthritis and back pain
  
  **psychiatric disorders**: depression, panic attacks and generalized anxiety disorder

• Significant positive associations between each pain condition and the psychiatric disorders

• The associations between the pain conditions and the anxiety disorders were generally larger than those between the pain conditions and depression.

*Williams et al. 2004*
Comorbid pain

Musculoskeletal pain

Low back pain

Neck pain

Migraine and pain

- Prospective follow-up study
- 1756 school children (mean age 10.8 years)
- Musculoskeletal pain
  - At baseline: 32.1%
  - After 1 year: 53.8%
  - After 4 years: 63.5%
- Neck pain was the most persistent
- Baseline headache once or twice a week was found to be a prognostic factor for pain persistence.

Finland, Turku

El-Metwally et al. 2004
Migraine and pain

- Headache was associated with low back pain in a cross-sectional population-based study of 9000 adolescents and young adults. Both conditions were associated with asthma.

- Individuals with headache were roughly twice as likely to report musculoskeletal symptoms as those without headache. The risk was similar in those with nonmigrainous and migrainous headaches. **Headache frequency** was a stronger predictor than headache type.

- Chronic spinal pain was associated with other chronic pain (arthritis, migraine, other headache and other chronic pain), as well as mood disorders, anxiety disorders, and substance use disorders, primarily alcohol abuse or dependence.


Migraine and epilepsy

- Chronic disorders with episodic manifestations
- Frequently occur together
- Share similar triggers and some clinical features
- Pathophysiology: Ion channels
- The therapeutic options for the disorders overlap.
Migraine and epilepsy

- The prevalence of migraine in patients with epilepsy 14-24%
  epilepsy in migraine subjects 1.1-17%
  
  Andermann and Andermann 1987,
  Leniger et al. 2003, Téllez-Zenteno et al. 2005

- Comorbidity of epilepsy included migraine, a national survey, Canada
  
  Hinnell et al. 2010

- A higher risk of unprovoked seizures among children with migraine with aura, a population-based case–control study, Iceland.
  
  Ludvigsson et al. 2006

Migraine and epilepsy

- Other studies have found no correlation between migraine and epilepsy, with conflicting results and questioning the existence of a definite comorbidity.
  
  Nuyen et al. 2006, Matias-Guiu et al. 1992,
  Tietjen et al. 2007, Brodtkorb et al. 2008
Migraine and epilepsy

- 9 Headache, 11 Epilepsy Centers, cross-sectional study, adults
- Headache 675
  migraine 68.8%
  Epilepsy 336
  Both disorders 156 (13.4%)
- The prevalence of H/E comorbidity
  30.0% from Epilepsy centers
  1.6% from Headache centers
- These rates are similar to those expected in general population.

Tonini et al. 2012

Temporal coincidence of migraine and epilepsy

Headaches attributed to epileptic seizures

- 7.6.1 Hemicrania epileptica
  Headache with migraine features lasting seconds to minutes synchronously with the partial epileptic seizure and is ipsilateral to the ictal discharge.

- 7.6.2 Post-ictal headache

Complication of migraine

- 1.5.5 Migraine-triggered seizures
  previously termed “migralepsy”
  A seizure fulfilling diagnostic criteria for one type of epileptic attack occurs during or within 1 hour after a migraine aura.

ICHD-II
Vascular disorders

- Stroke
- Myocardial infarction
- Peripheral artery disease

Migraine and ischemic stroke: Meta-analysis of studies before 2004

- 11 case-control studies and 3 cohort studies

Migraine 2.16 (1.9–2.5).
Migraine with aura 2.27 (1.61–3.19)
Migraine without aura 1.83 (1.06–3.15)

*Etminan et al. 2005*
Migraine and ischemic stroke: Meta-analysis

- 9 studies:
  six case-control
  three cohort

- The pooled relative risk
  1.73 (1.31-2.29)

- An increased risk
  women
  age < 45 years
  smokers
  oral contraceptives

Schürks et al. 2009

Migraine subtype and stroke: Meta-analysis

- 8 studies

- Migraine with aura
  2.16 (1.53-3.03)

- Migraine without aura
  1.23 (0.9-1.69)

Schürks et al. 2009
Migraine and other stroke subtypes: Meta-analysis

- 3 studies: an association between migraine and TIA
  
  \[2.34 \text{ (1.90-2.88)}\]
  
  *Higgins et al. 2003, Egger et al. 1997, Buring et al. 1995*

- 3 studies: an association between migraine and haemorrhagic stroke
  
  \[1.18 \text{ (0.87-1.60)}\]
  
  *Haut et al. 2006, Cook et al. 2002, Nightingale et al. 2004*

Migraine and myocardial infarction: Meta-analysis

- 8 studies: four cohort
  
  - The pooled relative risk
    \[1.12 \text{ (0.95-1.32)}\]

- 1 study: migraine with aura
  
  \[2.08 \text{ (1.30 to 3.31)}\]
  
  *Silberstein 2004*

*Schürks et al. 2009*
Migraine and angina pectoris: Meta-analysis

- 3 studies – slightly increased risk, especially in women
  \[1.29 \ (1.12 \text{-} 1.47)\]
  

- 1 study: migraine with aura
  \[1.71 \ (1.16 \text{-} 2.53)\]
  
  Silberstein 2004

Migraine and vascular death: Meta-analysis

- 5 studies
- The pooled relative risk
  \[1.03 \ (0.79 \text{-} 1.34)\]
- An increased risk: women migraine with aura

Schürks et al. 2009
Increased risk: **peripartum migraine**

<table>
<thead>
<tr>
<th>Vascular disorder</th>
<th>≈ RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain infarction</td>
<td>15</td>
</tr>
<tr>
<td>Myocardial infarction and heart disease</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolus and deep venous thrombosis</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
</tr>
<tr>
<td>Pre-eclampsia and gestational hypertension</td>
<td>1,8 - 5</td>
</tr>
</tbody>
</table>


Migraine and subclinical brain lesions

- Population-based study
- Migraine without aura 134
  Migraine with aura 161
  Controls 140
- Exclusion criteria:
  stroke
  TIA
  abnormal examination
- Neuroradiologist: MRI
  Neurologist: headache

Kruit et al. 2004
Migraine and subclinical brain lesions

- No differences in the overall infarct prevalence between migraineurs and controls.
- Cerebellar region migraine vs. controls OR = 7.1 (0.9-55)
- The highest risk: migraine with aura > 1 attack per month women OR = 15.8 (1.8–140)

*Kruit et al. 2004*

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Migraine and subclinical brain lesions

- An increased prevalence of infratentorial, mostly pontine, hyperintensities in migraineurs.
- The etiology: small-vessel disease or/and repetitive perfusion deficits.

*Kruit et al. 2006*
Migraine and patent foramen ovale (PFO)

<table>
<thead>
<tr>
<th>Migraine studies</th>
<th>Method</th>
<th>MA</th>
<th>MWA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del Sette 1998.</td>
<td>TCD</td>
<td>18/44 (41%)</td>
<td>/</td>
<td>8/50 (16%)</td>
</tr>
<tr>
<td>Anzola 1999.</td>
<td>TCD</td>
<td>54/113 (48%)</td>
<td>12/53 (23%)</td>
<td>5/25 (20%)</td>
</tr>
<tr>
<td>Schwerzmann 2005.</td>
<td>TEE</td>
<td>44/93 (47%)</td>
<td>/</td>
<td>16/93 (17%)</td>
</tr>
<tr>
<td>Dowson 2005.</td>
<td>TTE</td>
<td>220/370 (59%)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>overall</td>
<td></td>
<td>336/620 (54%)</td>
<td>12/53 (23%)</td>
<td>29/68 (17%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFO studies</th>
<th>Method</th>
<th>MA</th>
<th>MWA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilmshurst 2001.</td>
<td>TTE</td>
<td>42/120 (35%)</td>
<td>11/120 (9%)</td>
</tr>
<tr>
<td>Wilmshurst 2005.</td>
<td>TTE</td>
<td>59/119 (50%)</td>
<td>4/119 (3%)</td>
</tr>
<tr>
<td>Schwerzmann 2004.</td>
<td>OP</td>
<td>37/215 (17%)</td>
<td>11/215 (5%)</td>
</tr>
<tr>
<td>Reisman 2005.</td>
<td>OP</td>
<td>39/162 (24%)</td>
<td>18/162 (11%)</td>
</tr>
<tr>
<td>Morandi 2003.</td>
<td>OP</td>
<td>8/62 (13%)</td>
<td>9/62 (15%)</td>
</tr>
<tr>
<td>Post 2004.</td>
<td>OP</td>
<td>12/66 (18%)</td>
<td>14/66 (21%)</td>
</tr>
<tr>
<td>Azarbel 2005.</td>
<td>OP</td>
<td>22/66 (30%)</td>
<td>10/66 (15%)</td>
</tr>
<tr>
<td>overall</td>
<td></td>
<td>217/810 (27%)</td>
<td>77/810 (10%)</td>
</tr>
</tbody>
</table>

Migraine and PFO: Systematic review

- 18 observational studies
  - PFO and migraine \( \text{OR} = 5.13 (4.67-5.59) \)
  - PFO and migraine with aura \( \text{OR} = 3.21 (2.38-4.17) \)
  - Migraine and PFO \( \text{OR} = 2.54 (2.01-3.08) \)

low to moderate grade of evidence

- 6 studies of PFO closure suggested improvement in migraine, but had a very low grade of evidence.

Schwedt et al. 2008
Migraine with aura and R-L shunt

86 pts.  
77.9% females  
35.3 ± 12.4 years  

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of bubbles</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>1 (3) - 10</td>
</tr>
<tr>
<td>II</td>
<td>11-30</td>
</tr>
<tr>
<td>III</td>
<td>31-100</td>
</tr>
<tr>
<td>IV</td>
<td>101-300</td>
</tr>
<tr>
<td>V</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>

Bubble-test 80 pts.: 73.7%

New comorbidities

- Population-based study 31865 adult twins
- Previously documented diseases: asthma, epilepsy, stroke
- New conditions: kidney stone, psoriasis, rheumatoid arthritis and fibromyalgia.
- MA had more comorbidities than MO and females more than males.

Le et al. 2011
Migraine, lifestyle and socioeconomic factors

- Population-based study
- 31865 adult twins
- An increased risk of migraine:
  - lower level of schooling
  - lower level of education
  - retirement
  - unemployment
  - smoking

Le et al. 2011

Migraine and obesity

- Obesity was associated with increased frequency of attacks and might be a risk factor for migraine progression.

Bigal et al. 2006, Bigal et al. 2007
Comorbidities in cluster headache and migraine

Jasna J. Zivkovic-Trankovic, Tatjana D. Pekmezovic1, Ana L. Sunic2, Aleksandra P. Radojevic2 and Nadezda M. Stenić3

Headache Center, Institute of Neurology and Institute of Epidemiology Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

The most frequent comorbidities in CH patients

<table>
<thead>
<tr>
<th>Comorbid disorder</th>
<th>N (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic sinusitis (152)</td>
<td>81 (53.8%)</td>
</tr>
<tr>
<td>Hypertension (48)</td>
<td>7 (13.1%)</td>
</tr>
<tr>
<td>Cervical and thoracic spondylosis (62)</td>
<td>29 (48.2%)</td>
</tr>
<tr>
<td>Cervical spondylosis (143)</td>
<td>9 (6.3%)</td>
</tr>
<tr>
<td>Depression (P32) and anxiety disorders (P46)</td>
<td>4 (6.6%)</td>
</tr>
<tr>
<td>Diabetes mellitus (P13)</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td>Mitral and aortic valve (P12)</td>
<td>4 (5.3%)</td>
</tr>
</tbody>
</table>

130 pts 56.9%

The most frequent comorbidities in migraine patients

<table>
<thead>
<tr>
<th>Comorbid disorder</th>
<th>N (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (136)</td>
<td>136 (14.5%)</td>
</tr>
<tr>
<td>Carotid and cerebral arteries (62)</td>
<td>32 (12.4%)</td>
</tr>
<tr>
<td>Cervical spondylosis (M47.8)</td>
<td>61 (24.2%)</td>
</tr>
<tr>
<td>Depression (312) and anxiety disorders (464)</td>
<td>15 (5.9%)</td>
</tr>
<tr>
<td>Splenectomy (55)</td>
<td>45 (18.4%)</td>
</tr>
<tr>
<td>Irritability and other behavior (593)</td>
<td>36 (14.1%)</td>
</tr>
<tr>
<td>Migrainous tension (M88)</td>
<td>40 (15.4%)</td>
</tr>
<tr>
<td>Cervical spondylosis (M47.1)</td>
<td>27 (12.7%)</td>
</tr>
</tbody>
</table>

982 pts 56.7%

- Comorbid disorders in cluster headache patients were frequent and similar to those noticed in migraine patients, except chronic sinusitis and diabetes mellitus.