Role of gender and hormones in migraine

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In the past: Boehringer-Ingelheim, Ely Lilly, Endoceutics, HRA, MSD, Palatin TEVA, Warner Chilcott/Procter & Gamble, Zambon.
THE STORY OF MY INTEREST IN MIGRAINE

RE Nappi, 2021


**MIGRAINE IS FEMALE!**

- Migraine is more prevalent in boys than in girls during early childhood.
- After the onset of puberty and for the remainder of the lifespan, migraine is more prevalent in women than in men, with bimodal peaks of prevalence at 25 (±8.6) and 50 (±15.8) years of age.

### Table 1

GBD2019: Top level-3 causes of global disability (expressed as years lived with disability [YLDs]) by gender and age (data from [3, 4])

<table>
<thead>
<tr>
<th></th>
<th>Gender</th>
<th>Age</th>
<th>Cause</th>
<th>YLDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>All</td>
<td>15–49</td>
<td>Low back pain</td>
<td>7.7 [6.5–9.2]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gynaecological diseases</td>
<td>6.2 [5.1–7.3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Headache disorders</strong></td>
<td>6.0 [1.2–12.0]</td>
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<td></td>
<td></td>
<td></td>
<td>Depressive disorders</td>
<td>6.0 [4.8–7.5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–49</td>
<td>Gynaecological diseases</td>
<td>10.7 [8.7–12.9]</td>
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</tr>
</tbody>
</table>
THE CONCEPT OF MIGRAINE THRESHOLD

TRIGGERS
- Stressors
- Schedule Shifts
- Geoclimatic Changes
- Food
- Menstrual Cycle

TRAIT
- Familiarity
- Dysnociception
- Neuroendocrine Activity
- Personality / Mood Disorders
- Cardiovascular Risk Factors

MIGRAINE ATTACK

THRESHOLD

Nappi G, 1980’s
Women report migraine trigger factors to be provocative of their attacks more frequently than men, which may be related to a lower migraine threshold due to sex hormonal changes.
Migraine and relationship to menstrual window

Relationship between the menstrual cycle and migraine risk

menstruation

2 days before menstruation:
Migraine without aura:
• 1.7-fold $\uparrow$ to occur
• 2.1-fold $\uparrow$ to be severe

In the first 3 days of menstruation:
Migraine without aura:
• 2.5-fold $\uparrow$ to occur
• 3.4-fold $\uparrow$ to be severe

$>$50% of migraine without aura is strongly correlated to the menstrual cycle

Menstrual migraine can be highly debilitating and more difficult to treat

Estrogen drop during the last few days of the cycle is implicated in the pathogenesis of migraine

Frequent migraine attacks may occur during the hormone free interval in women on combined hormonal contraceptives

While absolute peak and day-to-day endogenous sex hormone levels were similar for migraineurs and controls, there were significant differences in the rate of estrogen withdrawal that were phase-specific (late luteal) and time-specific (2 days post peak). Furthermore, these differences occurred irrespective of whether migraineurs experienced headache within the cycle studied, suggesting neuroendocrine vulnerability in women with migraine.
Migraine, Hormonal Changes & Reproductive Milestones
WINDOW OF VULNERABILITY DUE TO THE HORMONE-FREE INTERVAL

“ESTROGEN WITHDRAWAL HEADACHE”
Headache lasts 4-72 hrs

“STATUS MIGRAINOSUS”
a severe, persistent headache that lasts for more than 72 hours, poorly responsive to analgesics

Hormone-Free Interval (HFI)

Last day of CHC

First day of CHC

Withdrawal Bleeding

Days with headache

The same paradigm may apply to menopause hormone therapy

Nappi & Berga, 2010
HORMONAL FLUCTUATIONS & MIGRAINE VULNERABILITY

Mid-cycle, late-luteal phase, menstrual withdrawal...

β-EP
5-HT
DA
NA/A
GABA
NO
Glu
PGs
Mg^{++}
Others

TRIGEMINO-VASCULAR SYSTEM

genomic & non-genomic effects

NEUROTRANSMISSION
VASODILATION
NEUROGENIC INFLAMMATION
OTHERS...

CORTICAL & LIMBIC AREAS

BRAINSTEM & MEDULLA

PERIPHERY

MIGRAINE ATTACK

Nappi & Tassorelli, 2011
Sex did influence Fos expression as confirmed by the significantly higher number of Fos-immunoreactive cells in cycling female rats in the PVH, SON, and SPVC when compared with intact male rats.
These data provide a support for the existence of a sexual dimorphism in NTG-induced neuronal activation, and they prompt a specific model for evaluating and modulating the influence of estrogens upon the cerebral structures implicated in the pathophysiology of migraine.
SEX & THE MIGRAINE BRAIN

There is more than estrogens: progesterone/its neurosteroid metabolites, androgens...

Pelvic pain/other pain conditions

PMS/PMDD
Interactions of estrogen, oxytocin & CGRP

Fig. 4 Oxytocin pathways. Oxytocin is synthesized in the paraventricular nucleus and supraoptic nucleus of the hypothalamus. The magnocellular oxytocin (MgnOT) neurons project to the posterior pituitary and secrete oxytocin into the peripheral circulation. Parvocellular oxytocin (ParvOT) neurons project to brain areas involved in central pain networks and to the spinal trigeminal complex, which receives primary sensory afferents from the trigeminal ganglion. TNC, trigeminal nucleus caudalis.
MENSTRUAL BLEEDING/PAIN AS AN INFLAMMATORY/VASCULAR PROCESS FACILITATING MIGRAINE?

- Dysmenorrhea
- Heavy Menstrual Bleeding
- Endometriosis
- CPP

Other catamenial symptoms

KEEP IN MIND: THE UTERUS CONTRACTS BECAUSE OF OXYTOCIN!

Yan et al, 2017

Henriet et al, 2012
A retrospective case control study was carried out on 100 women affected by migraine with typical aura (cases) and 200 age-matched women with MO (controls).

- Premenstrual syndrome was found to be much more common among the patients with MA (odds ratio (OR) 6.0; confidence interval (CI) 3.1-11.6).
- Menstrually triggered migraine was more frequently encountered among MO than among MA patients (MA 15.0%; MO 53.5%; OR 0.1; CI 0.1-0.3).
- In both forms of migraine, pregnancy had a favorable effect; however, a lower percentage of MA (43.6%) than MO patients (76.8%; OR 0.2; CI 0.1-0.5) showed improvement or remission.
- The use of oral contraceptives worsened migraine in MA more frequently than in MO patients (MA 56.4%; MO 25.3%; OR 3.8; CI 1.6-9.3).

*Granella et al, 2000*

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**KEEP IN MIND HORMONAL CONTRACEPTION IS A VERY COMMON TREATMENT FOR ENDOMETRIOSIS, DYSMENORRHEA, PMS, CHRONIC PELVIC PAIN!!!**
BEING A WOMAN IS A NON-MODIFIABLE CVD RISK FACTOR!

- Migraine amplifies many of the other well-established women’s risk factors for CVD, but further longitudinal studies are needed.
- Especially the occurrence of aura increases risks during pregnancy and menopause & under hormonal contraception and menopause hormone therapy.
- ISCHEMIC STROKE is around the corner and safety should be a priority.

Nappi et al, 2011; Sacco et al, 2017

Lee et al, 2017
Priority Areas in Sex and Gender Differences in Migraine Research, Care, and Education

“Stereotype of being emotional or week vs the evidence of a legitimate biological disease”

RE Nappi, 2021

Expanding current animal models
- Increase inclusion of female animals
- Expand pain and migraine model phenotypes
- Explore role of female hormones throughout animal lifespan

Broadening clinical studies
- Diversify ages and race/ethnicities of individuals enrolled in studies
- Include sex and gender differences in study design and analysis
- Improve understanding of the roles of social, epigenetics, and environmental factors in migraine
- Conduct longitudinal studies of hormones, migraine, and women
- Increase research on safety and efficacy of treatment options during pregnancy and lactation
- Improve understanding of the roles of sex and gender differences in comorbidities in migraine etiology and treatment

Increasing awareness to better identify and treat migraine
- Engage in more effective outreach and dissemination of current data regarding women and migraine for:
  - Hormonal therapies
  - Options during pregnancy and lactation

Improving quality-of-life measures
- Improve assessment of disability with inclusion of work, school, social life, and family
- Enhance understanding of migraine’s impact on workplace productivity

Destigmatizing migraine
- Improve employer understanding of migraine as a valid reason to miss work
- Increase rates of those seeking and continuing care
- Include menstrual and menstrually related migraine in the main text of ICHD
- Increase funding for migraine research and treatment development in areas that are important for women (e.g., safe treatments during pregnancy and lactation, issues related to perimenopause and menopause, and cardiac health)
- Increase funding and support of biobehavioral treatments and lifestyle factors
- Increase number of headache specialists

Schroeder et al, 2018
THANK YOU FOR YOUR ATTENTION!