Migraine and Ovarian Sex Hormones

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Objectives

- To discuss the relationship between migraine headache and changes in ovarian sex hormones that occur over the female life cycle
- To review an evidence based approach for the treatment of menstrually related migraine headache
Menstrually Related Migraine (MM)

- Attacks that occur on day -2 to +3 of menstruation in at least 2 out of 3 menstrual cycles and additionally at other times in the cycle.
- First day of the menstrual cycle is defined as day 1, and the day preceding menstruation is day -1.
Pure Menstrual Migraine

- Defined as attacks occurring exclusively on days -2 to +3 of menstruation in at least 2 of 3 menstrual cycles and at no other times of the menstrual cycle
Migraine and Female Sex Hormones

- Incidence of migraine equal in prepubertal boys and girls
- After menarche, incidence of migraine three times higher in women than men (25% vs 8%)
Migraine changes with hormonal events in the female life cycle

- Menstruation
- Pregnancy
- Oral contraceptive use
- Hormone replacement therapy
- Menopause
Migraine and Estrogen

In general:

- Migraine without aura associated with falls in estrogen (ie menstruation)
- Migraine with aura associated with high estrogen states (ie pregnancy, HRT)
- Reason unclear
Migraine and Menstruation

- 8% of women suffer from MRM
- 50% of women with migraine report an association between migraine and menstruation
- Increase in attacks seen 2 days before the onset of menstruation (1.7 X as likely) and the first 3 days of bleeding (2.5 X as likely)
- Migraine severity is greater perimenstrually
- MM are longer and associated with greater work related disability
- Acute attack treatment is less effective
- Associated with falling concentrations or withdrawal of estrogen that precedes menstruation
Migraine and the Birth Control Pill

- Migraine headache can worsen in some patients who use the BCP
- Women typically experience migraine attacks during the pill free week, when amounts of estrogen fall after 21 days of high concentrations
- Population studies reveal a significant association between migraine and BCP use
  - OR= 1.4
  - HeadHUNT study, Norwegian study of 14,000 women
Estrogen and Migraine with Aura

- High plasma concentrations of estrogen seem to be associated with attacks of migraine with aura.
- Migraine with aura can worsen or develop for the first time with use of combined oral contraceptives.
- Migraine with aura can occur for the first time during pregnancy.
- Migraine with aura associated with starting hormone replacement therapy - loss of aura occurs with lowering of dose or change in the route of delivery.
Migraine and Pregnancy

- For the majority of migraine sufferers, migraine improves during pregnancy
- Improvement begins in first trimester and is greatest in third trimester
  - 1st trimester: 47% improvement, 11% complete remission
  - 2nd trimester: 83% improvement, 53% complete remission
  - 3rd trimester: 87% improvement, 79% complete remission
- Likely due to loss of cyclical fluctuations in estrogen levels
- Migraine with aura can occur for the first time during pregnancy and can be complex
Study of 41 women referred for neurological consultation over a 2 year period for transient focal neurological deficits during pregnancy

- 34 of the 41 patients had migraine with aura (83%)
  - Migraine attacks prior to pregnancy present in 18 of 34 patients, 12 of 18 had migraine with aura
  - 5 of 34 patients had aura only (no headache)
  - 12 of 34 patients had aura followed by a non-migraine headache

- Symptoms occurred in first trimester in 17%, second trimester in 32% and third trimester in 51%

- Sensory aura was most common (79%), followed by visual aura (60%), and dysphasic aura (21%)

- Combination of visual and sensory aura occurred in 30%
Migraine with Aura and Pregnancy

- Typical aura can occur without headache or with a non-migrainous headache during pregnancy, making the diagnosis of migraine less obvious.

- Aura symptoms may be atypical
  - Sensory aura more common than visual aura in this selected sample.
Migraine and Pre-eclampsia

- Relationship between migraine, vasospastic disorders and ischemic stroke in young women
- Women with migraine are at increased risk of subclinical brain infarcts and white matter lesions
- Preeclampsia is a vascular disorder of pregnancy characterized by hypertension and proteinuria
- Vasospasm is a feature of preeclampsia, and preeclampsia has also been linked to an increased risk of ischemic stroke and heart disease
- Although the primary mechanisms of both migraine and preeclampsia are poorly understood, both are characterized by disordered vasoreactivity and abnormal platelet activity
Study comparing the cardiovascular risk profile of adult migraineurs to that of nonmigraineurs

Cases and controls identified through a population based study of a random sample of adults aged 20 to 65 living in 2 municipalities in the Netherlands

Participants were mailed a self administered questionnaire to obtain information about socioeconomic background, medical history and headache

The questionnaire was reviewed in person by a research assistant, who asked additional questions on the medical history and performed a simple clinical exam
Women with migraine were more likely to report a history of gestational hypertension than women without migraine.

Among 2517 women without migraine, 19% had gestational hypertension, in comparison to 482 migraineurs, of whom 27% had gestational hypertension.

Adjusted OR 1.63 (95% CI 1.2-2.1)

- Adjusted for age, socioeconomic status, smoking status and alcohol intake.
Migraine and Stroke in Pregnancy

- Pregnancy related stroke is rare but potentially devastating
- Association between migraine and stroke in pregnancy has been identified in a population based study
- Associations for various medical conditions and stroke
  - Migraine headache OR 16.9
  - Thrombophilia OR 16.0
  - Lupus OR 15.2
  - Heart disease OR 13.2
  - Sickle Cell Disease OR 9.1
Migraine and Menopause

- Although migraine prevalence decreases with advancing age, migraine can either regress or worsen at menopause.
- 13.7% of 556 consecutive post-menopausal women attending a clinic had headache; majority (82%) had headaches prior to menopause.
- Women with prior migraine generally improved with physiological menopause.
Migraine and Hormone Replacement Therapy

- Women’s Health Study demonstrated that current hormone replacement therapy was associated with higher rates of migraine headache than non-use, OR=1.41

- Some studies suggest that the oral route of administration has a greater propensity to worsen migraine than the transdermal route, which provides a more steady state concentration of estrogen
Migraine Prevalence in Male to Female Transsexuals

Tamara Pringsheim and Louis Gooren

Neurology 2004;63(3):593-594
Transsexualism

- Gender identity disorder
- Origin unclear
- Anatomic brain differences between transsexuals and nontranssexuals
MFTs: The Process

- Diagnosis made according to the Standards of Care of the International Harry Benjamin Gender Dysphoria Association
- Phase 1 Psychodiagnostic assessment
- Phase 2 One lives permanently in the role of the desired sex. Hormone treatment started.
- Sex reassignment surgery after successful completion of Phase 2
Hormonal Therapy

- suppression of original sex characteristics with anti-androgens
- to induce female sex characteristics - estrogens (usually 100 μg estrogen patch)
But do they have migraine?

- “refractory migraine headaches” cited as a contra-indication to sex hormone therapy
- 2/28 mentioned headaches as a side-effect of treatment
Division of Andrology, Gender Team

- Free University, Amsterdam
- Dr Louis Gooren, Endocrinologist
- Since 1975, over 900 MFTs and 300 FMTs have been treated
- Offer comprehensive care for 95% of transsexuals in the Netherlands
Methods

- Questionnaire developed using IHS criteria for migraine
- Questionnaire piloted in a headache clinic-determined to be sensitive tool in detecting migraine
- 8 multiple choice questions
- Diagnosis of migraine based on satisfying IHS criteria
To satisfy IHS criteria for migraine

- non-daily headache
- meet time criteria (4 to 72 hours)
- meet 2 of 4 pain characteristics
  - Pulsatile/throbbing
  - Moderate to severe intensity
  - Worsened by routine activity
  - Unilateral
- have 1 of 2 associated symptoms
  - Photophobia/photophobia
  - Nausea and/or vomiting
Methods

- Questionnaire distributed to MFTs at Department of Andrology, Gender Team Clinic
- Patients seen in follow-up after sex reassignment surgery over a 4 month period
Methods

- Calculated expected number of persons with migraine based on the Genetic Epidemiology of Migraine (GEM) study prevalence data for The Netherlands population by sex and 5 year age group.

- Calculated standardized prevalence ratios (SPRs) and 95% CI.

- For a SPR, a CI that does not include 100 is significant at the $p \leq 0.05$ level.
Results

- 50 questionnaires returned complete, representing an 80% response rate
- Average age 44 years, range 18 to 76
- All patients on hormone therapy—usually both an anti-androgen and estrogen
Results

13/50 (26%) met IHS criteria by questionnaire for Migraine or Probable Migraine

- Expected number of cases in genetic males from GEM study 3.62
- SPR 359.1 (95% CI 191 to 614)
- p=0.05
- Expected number of cases in genetic females from GEM study 12.3
- SPR 105.69 (95% CI 56.2 to 181)
- NS
Results

- 7/13 (54%) see flashing lights, zigzag lines or dark spots prior to the headache - suggests visual aura prior to headache
Results

- 15/50 (30%) have no headaches
- 22/50 (44%) have “tension-type” headaches
  - 19/22 no associated features
  - 19/22 mild pain intensity
  - 18/22 duration less than four hours
Discussion

- 26% of MFTs have migraine headaches
- Netherlands population based GEM study revealed a 1 year migraine prevalence of 25% in women and 7.5% in men
Discussion

- 54% of MFTs had visual symptoms prior to the onset of headache pain
- 31% of patients in Dutch study with migraine had attacks of migraine with aura
Discussion

Possible explanations for increased rates of headache in MFTs taking hormonal therapy include:

- structural differences in the transsexual brain
- migraine headache is part of the female gender role
- stress of gender reassignment triggers headache
Discussion

- High dose estrogen therapy may promote the development of migraine by its effect on nitric oxide
Nitric Oxide

- produced by NOS
- circulating NO arises mainly from vascular endothelium
- NO mediates endothelial dependent vasodilation
- NO levels influenced by presence of estrogen; women have higher circulating NO levels than men
MFTs, Vasodilation and Nitric Oxide

- MFTs have greater endothelium dependent vasodilation than control males
- Circulating NO levels are increased 72% in MFTs on anti-androgen therapy
Nitric Oxide and Migraine - Human Studies

- GTN, an NO donor, can induce headache
- Non-specific NOS inhibitor can abort spontaneous migraine attacks
Conclusion

- Similar migraine prevalence in Dutch genetic females and MFTs on high dose estrogen and anti-androgen treatment
- May be due to the effect of estrogen treatment on nitric oxide production, and the ability of this molecule to cause headache
Evidence Based Review: Acute Treatment and Prevention of Menstrually Related Migraine Headache

Tamara Pringsheim
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Treatment of Menstrually Related Migraine (MRM)

- Divided into two strategies:
  - Acute, abortive therapy taken at the time of the migraine attack
  - Short term preventative therapy taken perimenstrually for several days to prevent the migraine attack from occurring
Purpose of Guideline

- Given the greater severity, longer duration, and poorer response to analgesics of MM, information regarding the most effective treatment options for patients is important to clinicians.

- To provide a systematic review of the existing therapy trials for MM and make evidence-based recommendations for acute and preventative treatment of MM.

- Intended for primary care physicians, neurologists, and obstetrician-gynecologists who treat women with migraine.
Clinical Questions

- Which acute treatments for menstrually related migraine headache are effective in reducing pain?
- Which preventative treatments for menstrually related migraine are effective in preventing migraine?
- How should clinicians choose between management strategies for menstrually related migraine headache?
Description of the analytical process

- Review performed by three neurologists with expertise in headache and clinical epidemiology
- MEDLINE, EMBASE and the Cochrane Collaboration Library searched for RCTs relating to the clinical questions
- Search terms included migraine, menstrual disturbances, menstrual cycle, and menstruation, as well as terms describing specific types of clinical studies
- For inclusion, studies had to include more than 20 patients, be randomized, double-blind, placebo controlled or comparative studies
Assessment of Methodologic Quality

- Studies evaluated according to quality criteria based on the current methods of the US Preventive Services Task Force.
- Criteria serve to identify studies which are the least likely to be biased and the best representation of “the truth”.
- Studies are rated “good” if all the criteria are met.
- “Fair” studies do not meet all criteria but do not have a fatal flaw which invalidates results.
- “Poor” studies contain a fatal flaw.
Quality Criteria

- Adequate randomization
- Comparable groups
- Allocation concealment
- Confounders distributed equally
- Clear definition of interventions
- Absence of important differential loss to follow-up or overall high loss to follow-up
- Measurement instruments for outcomes are acceptable and applied equally; all important outcomes considered
- Masking of outcome assessment
- Intention to treat analysis
Recommendation Grades

- **A**: Strong recommendation that clinicians offer the treatment to eligible patients. Only made if there is good quality evidence of substantial net benefit from treatment.

- Substantial net benefit defined as a therapeutic gain (drug response minus placebo response) or absolute risk reduction of greater than 50%
Recommendation Grades

B: Strong recommendation that clinicians offer the treatment to eligible patients. Made if there is good or fair quality evidence of moderate net benefit from treatment.

Moderate net benefit defined as a therapeutic gain or absolute risk reduction of 20 to 50%
Recommendation Grades

- **C**: No recommendation for or against routine provision of the treatment as at least fair evidence shows that the balance of benefits and harms is too close to justify a general recommendation.

- **D**: Recommendation against providing the treatment as at least fair evidence exists that the treatment is ineffective or the harms outweigh the benefits.

- **I**: Insufficient evidence to recommend for or against the treatment due to poor quality or conflicting reports.
Results of Literature Search

- 170 abstracts found by combined searches
- 147 abstracts excluded; remaining 23 articles read in full
- 5 full text articles excluded
- 18 studies included in analysis; 10 pertaining to short-term preventative treatment of MRM, and 8 pertaining to acute abortive treatment of MRM
- Search re-executed prior to final submission of manuscript
- 1 further study found on acute treatment
- Searched 2007 abstracts of AAN, IHS, and ANA meetings
- 3 abstracts found; unable to obtain further information from study authors
Which acute treatments for MRM are effective in reducing pain?
Sumatriptan

- 4 studies comparing sumatriptan to placebo
  - 1 “good” quality
  - 3 “poor” quality

- Sumatriptan 100 mg vs placebo
  - Included 509 patients
  - 2 Hour Pain Free response
  - Summary therapeutic gain 34%
  - Summary risk difference for AEs 7% in favour of the placebo group

- Sumatriptan 50 mg vs placebo
  - Included 516 patients
  - 2 Hour Pain Free response
  - Summary therapeutic gain 25%
  - Summary risk difference for AE 6% in favour of the placebo group
**Sumatriptan**

- **Recommendation B:** We recommend that clinicians routinely offer sumatriptan to women with MRM for acute abortive therapy. We found good evidence that sumatriptan provides moderate benefit for pain relief and that the benefits outweigh adverse events.
Zolmitriptan

- 2 studies comparing zolmitriptan to placebo
  - 1 “fair”
  - 1 “poor”

- Zolmitriptan 1, 2.5 or 5 mg vs placebo
  - Include 1519 MM attacks
  - 2 Hour Pain response
  - Summary therapeutic gain 26%
  - Summary risk difference for AEs 20% in favour of the placebo group
Zolmitriptan

- Recommendation C: We make no recommendation for or against routine provision of zolmitriptan for acute treatment of MRM. We found fair evidence that zolmitriptan provides moderate benefit for pain relief but the balance of benefits and adverse events is too close to justify a general recommendation.
Mefenamic Acid

- 1 fair quality study comparing NSAID mefenamic acid to placebo
- Cross-over study of 24 patients
- 2 hour pain free rates were 67% in the mefenamic acid phase, vs 8% in the placebo phase
- \( p<0.05 \), therapeutic gain 59%
- Mild epigastric pain in 8% of patients in mefenamic acid phase, no other adverse events
- Recommendation B
Naratriptan

- 1 poor quality study comparing naratriptan 2.5 mg to placebo
- Recommendation I: Insufficient evidence to recommend for or against routinely offering naratriptan to patients with MRM due to poor quality of available evidence
Two good quality RCTs comparing rizatriptan 10 mg to placebo in the treatment of a single MM

Studies identical in design and published together

707 patients included

2 Hour Pain Response
- Summary therapeutic gain of 20%

No serious AEs; most common AEs reported were dry mouth, fatigue, paraesthesia and somnolence

Summary risk difference for AEs was 7% in favour of the placebo group

Recommendation B
Which preventative treatments for menstrually related migraine are effective in preventing migraine?
Transdermal estradiol

- 4 randomized double-blind cross-over studies comparing transdermal estradiol with placebo
  - 3 “fair” studies
  - 1 “poor” study
- Transdermal estradiol applied daily during perimenstrual period (days -2 to +5)
- Absolute risk reduction in 3 “fair” studies ranged from 23 to 66%, p<0.05
- Most significant side effect was the occurrence of “post-gel” migraine
- Recommendation B
Recommendation B

- **Frovatriptan**
  - “Good” quality study comparing frovatriptan 2.5 mg BID to placebo for 6 days perimenstrually in 546 patients
  - No difference in the rate of adverse events between groups
  - $p<0.0001$, ARR 26%

- **Naratriptan**
  - “Fair” quality study comparing naratriptan 1 mg BID to placebo for 5 days perimenstrually in 220 patients
  - No difference in rate of adverse events between groups
  - $P<0.05$, 50% reduction in number of MRMs
Recommendation I

- Nimesulide
- Magnesium
- Phytoestrogens
- Naproxen
How should clinicians choose between management strategies for menstrually related migraine headache?
How to choose?

- No trials comparing the relative efficacy of different treatment regimens for MRM
- Clinicians must base decision on:
  - Clinical judgement
  - Patient values
  - Cost
Clinical Considerations

- **Acute management grade B recommendations**
  - Sumatriptan
  - Mefenamic acid
  - Rizatriptan

- **Preventative management grade B recommendations**
  - Transdermal estrogen
  - Frovatriptan
  - Naratriptan

- **Medical co-morbidities**
- **Adverse effect profiles**
- **Individual preferences**
- **Cost**
Future Directions

- Review of 2007 abstracts
  - Short-term preventative studies of frovatriptan and zolmitriptan
  - Acute study of combination sumatriptan/naproxen tablet

- Trials of non-prescription analgesics

- Comparison of relative efficacy of treatment strategies

- Comparison of acute to preventative treatment strategies
  - Patient preferences
  - Compliance
Summary

- Migraine is more prevalent in women
- Relationship between migraine and ovarian sex hormones suggested in multiple ways
  - Menstruation
  - Birth control pill
  - Pregnancy
  - Menopause
  - Hormone replacement therapy
- Just part of the picture—many other molecules implicated in the pathogenesis of migraine—serotonin, dopamine, CGRP, substance P........to name a few
- Evidenced based treatments available for MRM; choice between agents should be clinically based