Sex Differences in Migraine

- Before puberty (10-14 girls), migraine affects both sexes equally
- Following puberty, migraine has strikingly higher prevalence in females than in men
- Female: male ratio – 2:1 to 3:1, peaks at midlife
- Female migraineurs have more symptoms (photophobia, nausea) and more migraine-related disability than male migraineurs
- Female predominance consistent across racial groups


**Sexual Dimorphism in Familial Hemiplegic Migraine**

- Rare autosomal dominant migraine with aura
- Danish study identified 147 affected FHM patients from 44 families
- Most often had all 4 typical aura symptoms: visual, sensor, aphasic, motor
- Headache present in 99% of FHM patients during attack
- **Female** (105) : **male** (42) = 2.5

Menstrual Migraine

- >50% of women with migraine report an association between migraine and menstruation
- Only migraine without aura
- Incidence greatest 2 days before menstruation and continuing through day 2-3 of bleeding
- More severe, disabling, and refractory to abortive medications than non-menstrually related
- IHS “Menstrual migraine” = attacks of migraine without aura which occur on day 1 ± 2 (i.e. days −2 to +3) of menstruation in at least 2/3 menstrual cycles (affects approximately 20% female migraineurs) [1st day of menstruation is day 1; no day 0]
Sex Steroids During Menstrual Cycle and Menstrual Migraine

Treatment with Progesterone Does Not Affect Menstrual Migraine

Daily injections of progesterone (25-75 mg) in sesame oil beginning 3-6 days before the expected onset of menstruation, adjusted to maintain plasma progesterone of 5-20 ng/ml (mid-luteal range)

Treatment with Estradiol Delays Menstrual Migraine

Estradiol valerate in oil (slow-release estradiol), 10 mg, i.m., 3-6 days before expected onset of menstrual bleeding

Plasma estradiol threshold = 0.05 ng/ml

Incidence of Migraine Relative to Menstrual Cycle Phases

- 38 women with 1-4 migraine attacks/month, 1 of which occurred perimenstrually
- Urinary metabolites collected daily
- Higher number of attacks late luteal/early follicular phase
- Lower number of attack during rising estrogen
- **No increased migraine in relation to postovulatory withdrawal**

Menopause

- Last menstrual period around age 51
- In perimenopausal years, orderly pattern of estrogen and progesterone secretion is lost
- Following menopause, lower levels of hormones fluctuate for 4-5 years; migraine may worsen but often progressively improves over time
- Migraine with aura unaffected by menopause

In postmenopausal women, fall in estrogen after 5 mg depo-estradiol triggers migraine in those with history of severe menstrual migraine but not in normal controls.

Sustained estrogen exposure necessary for estrogen withdrawal to provoke migraine attacks.

Threshold estrogen (0.05 ng/ml) same as in Somerville’s studies.

Cortical Spreading Depression

Depolarization

Decreased blood flow

CGRP
Substance P
Nitric oxide
Arachadonic acid

Vasodilation
Inflammation

Cranium
Meninges

Axon collateral of TGG neuron

Cortical Spreading Depression

Parasympathetic Efforent (superior palatine ganglion)

Parasympathetic Preganglionic (superior salivatory nucleus)

PAIN

Trigeminal Ganglion

Cortex
Thalamus

K⁺ AA H⁺ NO
Reduced CSD Threshold in Female Mice

Sex Differences in CSD in FHM Type 1 Mouse (R192Q mutation)

Homozygous R192Q CACNA1A gene (α1A subunit of Cav2.1 channels)

R192Q causes mild CSD

Topical KCl used to evoke CSD

Testosterone Suppresses CSD in FHM Type 1 Mouse (R192Q mutation)

- Subcutaneous testosterone pellet (0.1 mg/pellet, 21-day release)
- Testosterone propionate (1.2 mg)
- Subcutaneous flutamide (25 or 50 mg/pellet, 21-day release)

Case Report: Menstrual Hemiplegic Migraine Cured by Oophorectomy

- 48-year-old woman with premenstrual right arm and leg weakness, expressive dysphasia
- TAH-BSO
- Completely well with no subsequent recurrence of symptoms

MM – Perimenstrual Prophylaxis (NSAIDs)

- Naproxen (550 mg) b.i.d., 7-14 days, starting during the week before expected onset of menstruation
- Risks:
  - GI bleeding (consider gastroduodenal protection)
  - Medication-overuse headache
  - Fluid retention, edema → hypertension
MM – Perimenstrual Prophylaxis (triptans)

- Frovatriptan (load: 5 mg b.i.d. first day; 2.5 mg b.i.d. remaining days), 6 days, starting 2 days before expected onset of menstruation
- Naratriptan and zolmitriptan can also be used

MM – Estrogen Supplements

- Maintains luteal phase estradiol levels, preventing late luteal phase drop
- Women must be menstruating regularly (endogenous progesterone following ovulation provides endometrial protection)
- Estradiol gel 1.5 mg (1.5 g) daily, 7 days, starting between 2-5 days before expected onset of menstruation
- Estradiol transdermal system
Contraceptives – Progestin Only

- Ethinylestradiol-containing BCP’s contraindicated in migraine with aura due to 2-fold increased stroke risk; also contraindicated in clotting disorder, history of DVT, or cardiovascular risk factors (lipids, obesity, smoking, CRP)

- Progesterone only BCPs (“mini-pill”) safe alternative
  - Mini-Pill: Micronor, Nor-QD (norethindrone)
  - Implant (3 year): Implanon, Nexplanon (etonogestrel)
  - Depo: Depo-provera (medroxyprogesterone)

- Higher failure rate and slightly higher rate of ectopic pregnancy

- Alternatives: IUD, barrier contraceptives

- Levonorgestrel IUD (low systemic absorption) (Mirena, Skyla)
MM – Oral Contraceptives

- Oral contraceptives can be used to prevent pregnancy in most women with migraine; do not prevent migraine
- Risks of endometrial and ovarian cancer reduced; possibly reduce colon cancer risk
- Risk of breast, cervical, and liver cancer increased
- Estrogen withdrawal during hormone-free interval can trigger migraine
- Estrogen supplements can prevent (0.01 mg oral ethinyl estradiol, 0.9 mg oral conjugated equine estrogens, 0.1 mg/day estradiol patch, 2 g estradiol gel)
- Endometrial protection from progestagen in BCP
MM – Monophasic (Continuous) Low-Dose Combination Oral Contraceptives – Reduced Withdrawal Bleeds / Amenorrhea

• Contraceptive-induced amenorrhea reduces migraine frequency
• 84/7 regimen (4 withdrawal bleeds; Seasonique)
• No withdrawal bleeds (Lybrel; unscheduled bleeding in early cycles resolves with time; may “break with the bleed” - stop BCP for 3 days); by 10-12 months continuous use, 80-100% of women are amenorrheic

MM – Chemical Menopause: Leuprolide + “add-back”

- Leuprolide acetate 3.75 mg IM monthly
- Last 6 months estrogen-progestin “add-back” transdermal estradiol (E2) patches (0.1 mg/d) and oral medroxyprogesterone acetate (2.5 mg daily Provera)

Perimenopause

- Many women require treatment for vasomotor symptoms, usually with hormone replacement
- Oral estrogen can exacerbate migraine
- Non-oral routes: estradiol gel, estradiol transdermal system
- Endometrial protection with progestin necessary for women who have not had hysterectomy
  - Medroxyprogesterone acetate (2.5 mg/day)
  - Natural progesterone (100-200 mg/day)
  - Levonorgestrel IUD (low systemic absorption) (Mirena, Skyla)
  - 4% vaginal progesterone (Crinone) -- must apply daily, expensive

The End