Gender Differences in Neurological Disorders

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Topics

- Differences in Brain Anatomy/Physiology
- Pathological Differences in Presentation, Progression of various disease processes
- Management Based on Various Factors: side effect differences (tolerability), practicality and efficacy
- Public Health implications (example: stroke)
Physiologic Gender Differences:

- *University of Pennsylvania* study in 2013: Using diffusion tensor imaging of 949 individuals aged 8–22 years, mapped difference in male and female neural wiring, found
  A) **inter-hemispheric** connectivity was greater in women's and girls' brains
  B) **intra-hemispheric** connectivity was greater in the brains of men and boys. The effect was reversed in **cerebellar** connections

? multi-tasking vs. focus?  
? analysis vs. coordinated action?

Example: Studies using the Iowa gambling task, or Iowa Card Task, have examined cognitive reasoning and decision-making in males and females. A study in which participants of various age groups who were asked to perform the Iowa Card Task produced data showing that males and females differ in their decision making processes on the neurological level.

A) decision-making in females may be guided by avoidance of negativity

B) decision making in males is mainly guided by assessing the long term outcome of a situation (which helped their performance in this specific test)

MANY studies show that females remember rote lists and objects, with males’ memory being 3 dimensional or visual/spacial-based

Anatomical Differences:

- Amygdala
- Hippocampus
- Limbic system
- Orbital pre-frontal cortex
- Grey/white matter ratios – and rate of grey matter loss with development of neurological disorders
Disease processes will include:

- Alzheimer’s and other dementias
- Parkinson’s, Essential tremor
- Epilepsy
- Migraine and other headache conditions
- PNS (peripheral nervous system) topics to include neuropathies and myasthenic syndromes
- Stroke: prevention and life expectancy
- Other topics, Q & A
Note the generalized cerebral cortical atrophy.
ALZHEIMER’S DISEASE
Microscopic Disease

- Photomicrograph of entorhinal cortex in Alzheimer's disease. The neuritic plaque is composed of an amylloid core surrounded by dystrophic neurites. The dark flame-shaped fibrillar structures are neurofibrillary tangles, which are chiefly made up of paired helical filaments.
ALZHEIMER’S DISEASE (AD)

- Clinical:
  Subtle memory loss followed by slowly progressive dementia

  - **Language deficits** may be prominent, starting with word finding
  - **Apraxias** present – performing sequential tasks (dressing etc)
  - **Delusions** can develop LATER, with occasional hallucinations (early hallucinations suggest Lewy Body dementia)

- Genetics: Four different “susceptibility” genes: **apolipoproteins** *(apolipoprotein E4 homozygous: HIGH risk)*
Risk factors beyond Apolipoproteins:

- **AGE**: Incidence: 10% of pts > 70 yrs old; 40% if > 80 yrs old
  *(greatest risk factor is age)*

- **GENDER**: Women have a *higher* rate of AD, even when correcting for age and matching with Apolipoprotein type

As presented at AAIC (Alzheimer’s Association International Conference), July, 2015 –

A) Women with MCI (Mild Cognitive Impairment) decline dramatically faster in cognition, function and brain size.^

B) This is exacerbated post-surgically.^^

^ Lin, Duke University ADNI study, unpublished
^^Schenning, Oregon Health & Science, unpublished
(data available through the Alzheimer’s Association)
ANTICHOLINESTERASE – results in increase in acetylcholine in brain:

Aricept (donepezil) – prefer with breakfast due to GI, occasional insomnia when taken at night; don’t forget leg cramp side effect

Razadyne (galantamine) – VA formulary, nicotinic receptors

Exelon (rivastigmine) – GI side effects in oral form generally less in men, and the rivastigmine patch better–tolerated in both men and women

NMDA ANTAGONIST – Namenda (memantine) – usually well tolerated, adjunctive, *occasionally stimulating to the point of irritability

(recently available is combination memantine/donepezil combination)

Axona – medical food relying on alternative source via ketone bodies (proprietary formulation of coconut oil): GI side effects due to soy products and lactose
AD management implications re: gender

Should men and women be treated differently pharmacologically, or by other means (dietary, activities, etc.)?

More questions than answers at this stage regarding neuropharmacology, but INDIVIDUALIZING patient/family needs at forefront. Understand behavioral implications: Driving and other safety concerns, disinhibition, mood/affect.
An isolated Lewy body, a distinctive eosinophilic cytoplasmic inclusion body found in the substantia nigra of Parkinson's disease. Known to be more common in men — especially the bradykinetic form.
PARKINSON’S DISEASE

- Syndrome of a combination of
  - Tremor at rest – relatively slow
  - Rigidity
  - Bradykinesia
  - Characteristic disturbance of gait and posture
    (ABOVE ARE “CARDINAL” SIGNS)
  - Flexed posture of neck, trunk and limbs
  - Loss of postural reflexes
  - Freezing
  - Also dysautonomia (constipation, orthostatic bp drops, erectile dysfunction, flushing, etc.)
Levodopa (L–DOPA) = precursor of Dopamine
- Most effective for the bradykinesia – more common presentation in men
- The dopa decarboxylase inhibitor (carbidopa) reduces peripheral metabolism of L–DOPA
- “Sinemet” is a combination of this inhibitor and Levodopa: ‘sin’ (or without), ‘emet’ (or emesis)
  - While motor fluctuations prominent over time, better tolerability with higher dosing better in men (particularly GI)
  - Women may respond to VERY low doses (eg., ½ tab of 25/100 formulation
  - Administer WITHOUT food, and at least tid for best effect and prognosis
COMPLICATIONS OF L – DOPA

- To reduce wearing off effect – transient deterioration shortly before the next dose
- To prevent ON – OFF Phenomenon – abrupt but transient fluctuations that occur during day without warning
  - Reduce dose intervals
  - Take Sinemet at least ½ hour prior to meals, or 1 hr after
  - Restrict dietary protein diet (do reduce competition by various amino acids for the same carrier proteins that levodopa uses)
  - C–OMT (catechol O–methyltransferase inhibitor) can be taken with carb/levo, Or other meds.........
Role of Dopamine in the CNS

- Dopamine modulates various brain functions
  - Mood
  - Cognition
  - Motor function
  - Drive
  - Aggression
  - Motivation
PARKINSONS DISEASE Treatment

- **Dopamine agonists** – Good for mild to moderate Parkinson’s especially less than 70 yr old
  - Pramipexole (MIRAPEX), Ropinirole (REQUIP), Rotigotine (NEUPRO)
  - *** addictions problematic for women and men: dopamine stimulation pertains to pleasure-seeking. Gambling in both, with sexual-related addictive behaviors more prevalent in men and purchasing somewhat more frequent in women in clinical practice. “Punding” is a milder form of being stuck in the same activity.

**MAO-B inhibitors** (esp. Azilect): efficacy fair to good, excellent tolerability, some interactions including higher doses of SSRI’s

- **Amantadine** – MOA still not well understood, but helps some with motor fluctuations; hallucinations can develop in pts with PD dementia

- **Anticholinergic Drugs** – Cognitive, urological and other side effects so recommended for under 65 – helps tremor only

- *Rate of hallucinations: higher in all of the above compared to carb/levo (except Azilect)*
Essential Tremor

- No Parkinsonian features (no slowness or rigidity or gait disturbance)
- Faster than Parkinson’s tremor
- Bilaterally nearly symmetrical men’s greater predilection: hand involvement
- Can also involve the head and even voice: F>>M
  (Parkinson’s can involve jaw, however).
Many patients need none, as it is a condition, as opposed to a disease

Beta Blockers like ER form of propranolol (non-selective preferred in women, but men? – ED possible)

***May use prn short acting 10mg if side effects

Anticonvulsants such as mysoline (start with ½ of a 50mg pill at night and increase slowly), and even topiramate (less efficacy, however)
Migraine Prevalence Compared With Other Neurologic Diseases

MS = multiple sclerosis; PD+HD = Parkinson disease + Huntington disease; AD = Alzheimer’s disease.

Migraine Is a Highly Prevalent Medical Disorder

28 million US migraine sufferers

1-yr prevalence of migraine in the US 1999 (%)

Overall: 12.6%
Females: 18.2%
Males: 6.5%

Migraine: A Common Episodic Headache Disorder

- **Neurologic disorder**
  - Strong genetic component (up to 50%)

- **Global prevalence:**
  - Women: 15%–17%
  - Men: 6%–9% **AND** lower rate of diagnosis (misdiagnosis with cluster)

- **2 major subtypes**
  - Without aura (~75%)
  - **With aura (~25%) – occasionally without headache when later in life**

- **Burden**
  - Among the world’s 20 most disabling diseases (WHO)
  - Indirectly costs employers up to $13 billion per year
  - Direct medical costs exceed $1 billion per year

**WHO = World Health Organization.**
Lifetime incidence of migraine: closer to even later in life

Figure 1. Migraine prevalence by age. Prevalence increased from 12 to 38 years of age in both females and males; the peak was considerably higher among females.
Migraine Is an Episodic Recurrent Headache Lasting 4-72 Hours with:

**Any 2 qualities:**
- unilateral pain
- throbbing pain
- pain worsened by movement
- moderate or severe pain

**Any 1 of these:**
- nausea
- vomiting
- photophobia and phonophobia

**IMPORTANTLY,** tension-like features such as posterior head and neck pain can also be present in a headache that meets IHS criteria for migraine.

The Migraine Process: Activation of the Trigeminal Nucleus Caudalis

- CNS dysfunction
- Vasodilation of dural blood vessels
- Local release of CGRP
- Activation of primary afferent neurons of trigeminal nerve
- Trigeminal ganglion
- Trigeminal nucleus caudalis
Migraine: older Single agent, e.g., aspirin, NSAIDs, COX-2’s, ergotamine alone or in combination, Parenteral dihydroergotamine

Migraine combinations 1. aspirin and caffeine and acetaminophen, 2. codeine and acetaminophen. 3. Combinations of isometheptene, 4. ‘fiorinal’ or ‘fioricet’ (**avoid frequent dosing of butalbital compounds due to high rate of rebound)

ACUTE TX: (and preferred)
Triptans such as sumatriptan, naratriptan, rizatriptan, zolmitriptan, almotriptan, eletriptan, combination suma/naproxen,

Also – remember injections - suma, nasal spray (sumatriptan and zolmig), dissolving (rizatriptan, zolmig)

****with men, always keep ‘transportability’ in mind****
<table>
<thead>
<tr>
<th>Prophylaxis</th>
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<tbody>
<tr>
<td><strong>b-blockers</strong></td>
<td>Propranolol - beware in men (ED)</td>
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<tr>
<td></td>
<td>Also low HR, with its implications</td>
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<tr>
<td><strong>TCAs</strong></td>
<td>Amitriptyline, Nortriptyline – wt gain,</td>
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<tr>
<td></td>
<td>orthostasis</td>
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<tr>
<td><strong>CCBs</strong></td>
<td>Verapamil – ** works well if aura,</td>
</tr>
<tr>
<td></td>
<td>note that constipation is common</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Sodium Valproate – OK in men</td>
</tr>
<tr>
<td></td>
<td>NOT OK in women of reproductive age</td>
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<tr>
<td></td>
<td>Topiramate (cognition, wt loss)</td>
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Becker (1999); Bartleson (1999)
Sexual Dysfunction: pharmacologic categories relevant to neurology and psychiatry

- **Tricyclic Antidepressants (TCAs)**
  - Stimulation of 5HT2A receptors
  - Inhibits erection > ejaculation (Reduction of lubrication in women)

- **Selective Serotonin Reuptake Inhibitors (SSRIs)**
  - Increases serotonin levels in both sexes
  - May decrease sex drive
  - **Impairs orgasm (primarily delay)
  - 5HT2A Agonist
Substances Related to Sexual Dysfunction (various neurological and psychiatric conditions)

- Antidepressants
- Lithium
- Sympathomimetics
- $\alpha$ and $\beta$ – adrenergic antagonists
- Anticholinergics
- Antihistamines

- Anti-anxiety agents
- Alcohol
- Opioids
- Hallucinogens
- Cannabis
- Barbiturates
- Sedative hypnotics
Cluster Headaches

- Brief (almost always less than an hour)
- Almost always male
- Unilateral
- Most frequently at night, often after etoh or tob
- “Clustering” pattern
- Similar prophylaxis to migraines, but consider mini–prophylaxis with steroids
- Injectable sumatriptan (imitrex) FDA approved, and home oxygen sometimes used to treat an attack
SEIZURES / EPILEPSY
CAUSES OF STATUS

- Anticonvulsant withdrawal
- Medical Noncompliance
- Metabolic Disturbance
- Drug Toxicity
- CNS Infection or tumors
- Refractory epilepsy
- Head trauma
Gender differences in presentation and prognosis for epilepsy

- Women have a higher rate of generalized epilepsies.

- Men have a higher incidence of status epilepticus, sudden unexpected death in epilepsy (SUDEP), prognosis and mortality for any reason related to epilepsy/seizures.

Anticonvulsant choices:
Special Issues Related to Gender

Contraception:
phenytoin, carbamazepine, lamotrigine all lower estrogens

Non–issue in men
GENERALIZED: **Valproic Acid**
(contraindicated in women of childbearing age due to neural tube defects) – but studies show it to be the most effective for primary generalized epilepsies such as tonic–clonic convulsions.

**Excellent choice for men.** Side effects include dose–related tremor and thinning of hair, usually at levels of greater than 100 mcg/dl

NOTE: ethosuximide is an alternative for absence epilepsy (which is also a generalized epilepsy)
Partial-onset (+/- secondary generalization):
phenytoin, carbamazepine, lamotrigine,
*levetiracetam, gabapentin, pregabalin, topiramate, and oxcarbazepine

*levetiracetam (Keppra) has gained in popularity tremendously in recent years due to safety, efficacy and minimal Rx interactions – BUT behavioral issues of irritability need to be taken into account.
MULTIPLE SCLEROSIS

Characteristics

◦ Most common young adult neuro disability (after trauma)
◦ Presentation: Weakness (35%) Optic neuritis, (36 %) Sensory Disturbance, (37%) Ataxia (11 %) Diplopia (15%)

◦ Familial Preponderance
◦ Whites > other ethnic races (esp. northern European, Irish)
◦ Location/Risk : Increased in temperate climate

◦ Females = incidence is 2 x Males, but primary progressive and transition to secondary progressive: male predilection.
◦ Relapsing forms more common in women – stakes are higher in treating, as meds likely to make more of a difference.
MULTIPLE SCLEROSIS

Reduce attack frequency and disease burden w/ immunomodulatory agents.

**Interferons** Beta–1–a (Avonex once/wk IM) (Rebif T.I.W. sq)

Beta–1–b (Betaseron every other day)

**Glatiramer Acetate** (daily Copaxone)

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recently, chemotherapeutics:

**Tysabri:** JC virus

**Aubagio:** pregnancy category X

**Gilenya:** cardiac monitoring

**Tecfidera:** flushing, leucopenia

**Lemtrada:** thyroid disease

common; primary progressive tx?
1. Type 2 diabetic polyneuropathy develops at a younger age in male patients than female patients (average age 63 vs 67).*

2. Male patients less likely to be diagnosed with type 2 DM**

*Aaberg, etal, J diabetes complications, 2008, Mar–Apr

Trends in diabetes prevalence in adults age 20+ by Sex
NH – non–Hispanic.
Therefore, in neuropathy

- Look for **DM** assertively in men who present with foot numbness, considering **OGTT’s**
- Always consider **ETOH use hx** spanning across a **lifetime**, with implications on other nutritional aspects (of course B12).
- American Academy of Neurology (AAN) 2009 recommendations:

  "The tests with the highest yield of abnormality are **blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis** (Class III). Patients with distal symmetric sensory polyneuropathy have a relatively high prevalence of diabetes or prediabetes (impaired glucose tolerance), which can be documented by **blood glucose or GTT** (Class III)."
Etiol: – RECEPTOR ANTIBODIES
  ◦ Decreased numbers of acetylcholine receptors due to autoimmune destruction

Epidemiology
  ◦ Bimodal peak of incidence in younger women (second and third decades) and older men (fifth and sixth decades).

THYMUS:
  ◦ Surgical removal associated with improvement in disease severity IN YOUNG PATIENTS (<50)
  ◦ Thymic abnormalities are either hyperplastic or neoplastic.
  ◦ Neoplasms occur in about 12 percent of patients—locally invasive epithelial cell tumors (thymomas) – prompting surgery – even in older patients
**MYASTHENIA GRAVIS**

- **History**
  - Diplopia, ptosis, weakness (**Ocular motility involvement**)
  - Fluctuation in fatigue worse with repetition and better with rest

**Differential diagnosis of WEAKNESS:**
1. ALS (somewhat more common in men),
2. Lambert–Eaton Myasthenic Syndrome (much more common in men), and
3. myopathies (gender variation based on type)

- **DIAGNOSIS**
  - Edrophonium chloride (Tensilon) injection, Clinical Suspicions
  - Anti–AchR radioimmunoassay
    - A Positive test is Dx, A neg test does not exclude disease
  - Repetitive Nerve Stimulation: look for decremental (fatigue) response
  - Single Fiber electromyography

- **TREATMENT**
  - Acetylcholinesterase inhibitors (mainly pyridostigmine)
  - Thymectomy
  - Corticosteroids
  - Cytotoxic Therapies → Azathioprine, cyclosporine
  - Plasma exchange and intravenous pooled immune globulin (IVIg) for urgencies or exacerbations
Stroke

Ischemic 85%

Can a higher rate of consultation with physicians (such as primary care wellness visits) have an favorable impact on a disorder with high morbidity and mortality?

Stroke rates (and other cardiovascular diseases) and gender life–expectancy gap: implications of differences in the rate of consultation?
Estimated direct and indirect costs (in billions of dollars) of major cardiovascular diseases and stroke (United States: 2010). Source: NHLBI.
Gender differences (in studies around 2000)....

Three times as many men as women had not seen a doctor in the previous year (24% vs. 8%). One of three men had no regular doctor, compared with one of five women (33% vs. 19%).

Uninsured men were at least three times as likely as insured men not to have gotten care when needed, filled a prescription because of the cost, or seen a specialist (28% vs. 9%).

Among men age 50 and older, 60 percent had not been screened for colon cancer and 41 percent had not been tested for prostate cancer in the year prior to the survey.

2013 study: men's consultation rates were over 30% lower than women's age 16–60

- there was very little difference in childhood and older age, and much higher rates of consulting in women than men during the reproductive and mid-life years.

- consultations for reproductive reasons only partially explained the large gap in consulting between men and women in mid-life.

- The gender difference in consulting also varied by deprivation status, reflecting a socioeconomic gradient in consulting rates among women but not men.
Annual rate of all first-ever strokes by age, sex and race (GCNKSS: 1999).

Source: GCNKSS unpublished data. Note: rates for ages 45-54 for black men and women and for black men 75 and over, are considered unreliable.
CVD and other major causes of death: males (United States: 2006). Source: NCHS and NHLBI.
Men and women present differently with neurological disorders

Treatment options, of course, need to be tailored to needs – and this includes gender differences

We have a responsibility as physicians and leaders to foster patients’ use of resources to maximize health. This benefits individuals and families, and will hopefully favorably impact public health
THANKS!! Questions.....