Sex Differences in the Risk for Alzheimer’s Disease – Are Women at Greater Risk?

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Outline

• Are women at greater risk of Alzheimer’s disease (AD)?
• Sex differences in brain structure and function
• Biological explanation for the sex differences
• Conclusions and discussion
Are Women at Greater Risk of Alzheimer’s Disease?
More women than men have AD

Adults Aged 65 and Older with Alzheimer’s Disease,* By Sex, 2011

- Male: 34.6%
- Female: 65.4%

*Estimates are from the Chicago Health and Aging Project incidence rates converted to prevalence estimates and applied to 2011 U.S. Census Bureau estimates of the population aged 65 and older.

Stockholm, Sweden

Cambridge, U.K.

South-Western France

Europe, pooled data

Framingham, MA

Rochester, MN

Edlund et al, 2002, Arch Neurology
Reasons for disparities (US vs. Europe)

- Small sample sizes at upper age ranges
  - Unstable estimates
- Different diagnostic criteria
  - AD vs. other dementias
- Social, cultural, historical events
  - World War II and Cold-War
  - Education
  - Would European countries see a similar sex difference in future generations?

Mielke et al., 2014
Clinical differences

• Rate of progression
  • Risk of MCI higher in men or equivalent across sexes?
    (Sachdev et al., 2012; Roberts et al., 2012)
  • Some studies suggest women progress faster
    (Roberts et al., 2014; Tschanz et al., 2011)

• Behavioral symptoms
  • Anxiety/delusions - women (Steinberg et al., 2006)
  • Apathy and agitation -- men

• Response to treatment
  • Cholinesterase inhibitor/memantine use associated with slower decline in women, especially APOE E4 carriers
    (Mielke et al., 2012)
  • Intranasal insulin studies of MCI and AD patients show sex differences in treatment response (Claxton et al., 2013)
Sex Differences in Brain Structure and Function
Brain differences in men and women

(Scientific American MIND, May/June 2010)
Structural differences

• Men have a larger head size and cerebral volume
  • Withstand more pathology vs. women?
  • Women have higher odds of clinical diagnosis of AD with similar pathology (Barnes et al., 2005)

• But, among cognitively normal individuals, men have faster age-associated brain volume decline vs. women

• Women have higher percentage of grey matter; men of white matter (Giedd et al., 1997)
Structural differences, cont.

- **Lentini et al., 2013**: XXY males, XY males, XX females
  - Cerebellar and precentral grey matter volumes related to X chromosome dosage
  - Sex differences in the amygdala, parahippocampus, and occipital cortex linked to testosterone levels
    - No selective effect, testosterone-independent, of Y chromosome

- **Ingalhalikar et al., 2014**: Structural connectome with DTI
  - Men had greater within-hemisphere connectivity; women had greater between-hemisphere connectivity
    - Male brains structured to facilitate connectivity between perception and coordinated action
    - Females to facilitate communication between analytical and intuitive processing modes
Sex differences in the structural connectome

Ingalhalikar et al., 2013
Women are mosaics of X

(Courtesy of Dr. Miller, 2013)
Laterality in X inactivation: brain cortex (mice)

Red and green dots indicate paternal or maternal inheritance of X chromosome

Wu et al., 2014
NIA-AA Preclinical AD staging in relation to AD biomarker model

Sex differences in preclinical AD pathology

Jack et al., 2015
Structural Differences Summary

- Men and women clearly have differential development in brain structure and function
  - Based on amyloid and neurodegeneration markers, are men clinically over-diagnosed as AD?

- How are these sex differences longitudinally associated with risk and progression of AD?
  - Prenatal to old age
  - Effects of hormones and gender-specific factors
Biological Explanations for the Sex Differences
Hormones

- Estrogen is a critical signaling molecule in the brain.
- Estrogen receptors (ER) are widely distributed in brain for both sexes.
- ER ratios change with age in hippocampus.
- "Healthy cell bias of estrogen" (Diaz Brinton, 2008)
  - Only if neurons are healthy at the time of estrogen exposure, response is beneficial.
- Low testosterone and cognition in men.
Sex hormones in men and women over life

(Ober al., 2008)
Bilateral oophorectomy and risk of cognitive impairment or dementia

HR = 1.6 (1.1 – 2.4)

Rocca et al., 2007
Genetics

• APOE E4 allele – strongest known genetic risk factor for sporadic AD
  • Greater effect on women:
    • Risk of AD
      (e.g., Farrer et al., 1997; Parami et al., 1996; Bretsky et al., 1999; Altman et al., 2014)
    • Lower hippocampal volume (Fleisher et al., 2005)
    • Lower cortical thickness (Liu et al., 2010)
    • Greater amyloid plaque and neurofibrillary tangle pathology (Corder et al., 2004)
  • APOE*Estrogen – Estrogen associated with less cognitive decline in E4 non-carriers, but not E4 carriers (Jacobs et al., 2013)
APOE and risk of AD

(Farrer et al., 1997)
Additional risk factors for men and women

- **Both**
  - Education < 12 years
  - Memory concerns
  - Stroke
  - Atrial fibrillation
  - Late-life Diabetes

- **Women**
  - Current smoker
  - Midlife hypertension
  - Midlife high cholesterol
  - Midlife diabetes

- **Men**
  - BMI ≥ 30
  - Never married/widowed
  - Head trauma (?)
Conclusions and Discussion
Sex differences in AD

- Women have a higher prevalence of AD; incidence is equivocal
- Evidence for sex differences in brain pathology
  - Still unsure how this relates to clinical phenotypes
- Some risk factors are sex specific (e.g., pregnancy, oophorectomy, estrogen)
- Many risk factors are different in men and women
- Need to also understand the gender-associated effects on AD and AD pathology
Thank you