Sex Differences in Multiple Sclerosis: Clinical, Imaging, and Pathology

Sex Differences and Implications for Translational Neuroscience Research – A Workshop
Forum on Neuroscience and Nervous System Disorders
Institute of Medicine of the National Academies

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Multiple Sclerosis
Background

♦ US prevalence approx 1/1000
♦ Typically diagnosed between the ages of 25-45
♦ The most common, non-traumatic cause of disability in young adults
♦ By 15 years from onset, ~ 75% have a progressive course and moderate-severe disability
Multiple Sclerosis
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♦ Relapsing-remitting (85%)
♦ Secondary Progressive (SPMS; 75-80% of RRMS)
♦ Primary Progressive (PPMS, 10%)
♦ Progressive Relapsing (5%)

♦ Neuromyelitis optica: rare (~1%) CNS demyelinating disorder
  – Optic neuritis, transverse myelitis, atypical brain lesions
Multiple Sclerosis
Measuring Disease

♦ 2 categories of measuring MS:
♦ Active inflammation:
  − Clinical relapses
  − Gadolinium-enhancing lesions
♦ Accumulated injury
  − Disability progression
  − MRI lesion burden: T2 lesions, T1 lesions
  − Brain atrophy: whole brain, white matter, gray matter
  − Advanced imaging: magnetization transfer ratio, diffusion-weighted imaging

31 yo male healthy control
36 yo woman RR-MS (2 yrs)
43 yo woman SP-MS (19 yrs)
Multiple Sclerosis Sex Differences
Clinical Observations

- 2-3x more common in women (Orton, Lancet Neurol 2006; Alonso, Neurol 2008; Debouverie, EJN 2008)
  - Ratio decreased with older age (Marrie, Neurol 2010)
  - Equal ratio among PPMS (Edan, JNS 2009)
- Neuromyelitis optica: >3 more common in women
- Peak incidence is earlier in women: 35-39 yrs; men: 45-49 yrs (Marrie, Neurol 2009)
  - Peak prevalence is similarly shifted – women: 45-59 yrs; men 55-69 yrs
- Prevalence is increasing
  - Incidence roughly stable
  - Less diagnostic delay and greater survival (Ekestern, EJN 2004; Bronnum-Hansen, Brain 2004; Marrie, Neurol 2005)

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<tr>
<th>Age, y</th>
<th>Rate ratio</th>
<th>95% CI</th>
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<td>&gt;65</td>
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<tr>
<td>Total</td>
<td>3.15</td>
<td>2.75-3.80</td>
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</table>

Marrie, Neurol 2010
Multiple Sclerosis Sex Differences
Clinical Observations

- Prognosis (relapses, progressive disability): variable observations
  - Females have favorable prognosis (Confavreux, Brain 1980; Detels, Arch Neurol 1982; Wolfson, Neuroepid. 1987; Weinshenker, Brain 1991; Runmarker, Brain 1993; Trojano, JNNP 1995; Kantarci, Neurol 1998; Confavreux, Brain 2003; Wolinsky, MS and Demyelinating Diseases [book] 2006; Khaleeli, Ann Neurol 2008)
  - No sex difference observed in neuromyelitis optica

- Relationship to sex hormones:
  - Decreased relapse rate during pregnancy – particularly during third trimester – then rebounding after pregnancy (Confavreux, NEJM 1998; Alonso, Arch Neurol 2005)
  - Effect of oral contraceptives:
    - Lower incidence of MS (Villard-Mackintosh, Contraception 1993; Alonso, Arch Neurol 2005)
    - No effect (Thorogood, Br J Obset Gyn. 1998; Hernán, Neurol 2000)
    - Increased risk in long-term users (Hernán, Neurol 2000)

Confavreux, NEJM 1998
Multiple Sclerosis Sex Differences
MRI Measures

Active inflammation:
♦ Early and smaller studies (n = 50-413) found gadolinium-enhancing lesions more commonly in women. (Weatherby, J Neurol 2000; Pozzilli, EJN 2003; Tomassini, JNNP 2005)
♦ Later, larger studies (n = 763-1328) found no sex difference in gadolinium-enhancing lesions (Barkof, Neurol 2005; Antulov, Mult Scler 2009)

Accumulated Injury:
♦ T2 lesions: no sex difference, after covariate adjustment (Tedeschi, Neurol 2005; Li, Neurol 2006, Antulov, Mult Scler 2009)
♦ T1 lesions: no sex difference in RRMS, SPMS; greater T1 lesion volume in male PPMS (Pozzilli, EJN 2003; Van Walderveen, Arch Neurol 2001; Antulov, Mult Scler 2009)
♦ Atrophy: no sex difference in cross-sectional studies or longitudinal studies (Kalkers, Arch Neurol 2002; Tedeschi, Neurol 2005; Giorgio, Neuroimaging Clinics N Am 2008; Antulov, Mult Scler 2009)
♦ Conflicting results with gray matter atrophy: greater in men (Antulov, Mult Scler 2009) or equal in men and women (Giorgio, Neuroimaging Clin N Am 2008)
♦ MTR, diffusion-weighted imaging: no sex difference (Antulov, Mult Scler 2009)

“It appears appropriate to conclude that gender does not seem to exert independent effects on morphologic changes of the brain as detected by MRI.” (Fazekas, JNS 2009)
Multiple Sclerosis Sex Differences
Histopathology

Only a few pathological studies have evaluated sex, but none have found an effect.

♦ Active inflammation:
  - Equal number of macrophages/microglial cells and T-cells in both MS lesions or normal-appearing white matter (Kuhlmann, JNS 2009)

♦ Tissue damage:
  - Equal number of amyloid-precursor protein-positive spheroids (Kuhlmann, Brain 2004)
  - Equal reduction in axonal density (Kuhlmann, JNS 2009)
  - No difference in number, type, or distribution of cortical lesions (Wegner, Neurol 2006 [reanalyzed in Kuhlmann, JNS 2009])

♦ Repair:
  - No difference in number of oligodendrocyte precursor cells, differentiating oligodendrocytes, or mature oligodendrocytes (Kuhlmann, Brain 2008 [reanalyzed in Kuhlmann, JNS 2009])
  - No difference in remyelinating lesions (Goldschmidt, Neurol 2009)

♦ Only pathologic sex difference: lower fiber density in spinal pyramidal tracts in men (Ganter, Neuropathol Appl Neurobiol 1999)
Multiple Sclerosis Sex Differences

Clinical Trials

Vast majority of clinical trials have found no effect of sex on outcome

♦ Many trials had pre-planned covariate analysis for sex
  – Most were silent on effect of sex (Sibley, Neurol, 1993; Arnason, Neurol 1999; Comi, Ann Neurol 2001; Clanet, Neurol 2002; Filippi, Lancet 2006)
  – Some reported no effect (Beck, Ann Neurol 2002; Kappos, Neurol 2006; Rudick, NEJM 2006)

Notable exceptions:

♦ Interferon (Rebif) secondary progressive MS trial: only women had slowed progression of disability (SPECTRIMS Study Group, Neurol 2001)
♦ Interferon (Betaseron) secondary progressive MS trial: only women had slowed progression of disability (Kappos, Neurol 2001)
  – Unclear if either study adjusted for other covariates
  – A 3rd interferon (Betaseron) secondary progressive MS trial found no effect of sex (NA Study Group on IFNβ-1b in SPMS, Neurol 2004)
♦ Glatiramer acetate primary progressive MS trial: post-hoc analysis showed only men had slowed progression of disability (Wolinsky, Ann Neurol 2007)
  – Difference persisted after covariate adjustment (i.e. age, baseline disability, disease duration)
♦ Other interferon and glatiramer acetate trials showed no effect of sex (Rudick, Arch Neurol in press)

No relapsing remitting MS trial has shown a differential effect of sex on relapses
No clinical trial has shown a differential effect of sex on any MRI outcomes
(Wolinsky, JNS 2009)
Summary

Sex Differences in Multiple Sclerosis

♦ MS is 2-3x more common in women
  - Onset is later in men, and more likely to be PPMS
♦ Women may have a better prognosis
  - Differences decrease after adjusting for age at diagnosis and disease course (PPMS).
♦ Pregnancy decreases disease activity
  - Unclear effect of oral contraceptives
♦ In contrast to observations in smaller studies, large MRI studies suggest no effect of sex on MRI measures of either inflammation or tissue injury
♦ Pathology shows virtually no effect of sex
♦ Most clinical trials showed no effect of sex
  - A few post-hoc analyses found sex to be a significant covariate, but in different directions and not consistently between trials

Altogether, with the exception of incidence, there is little clinical evidence to suggest a sex difference in multiple sclerosis.