Search for Male/Female Parallels and Precedents Found in Cardiovascular Disease

Differences between women and men in health and disease have been gaining attention slowly. Cardiovascular diseases, the leading causes of morbidity and mortality, were widely recognized in men but *not* in women until studies were designed to address research questions in women and data were critically evaluated separately for the sexes.

In terms of the brain, neuroscientists report specific anatomical, molecular, functional and cognitive differences between males and females in several animal species including humans (1, 2, 3, 4). What do biologic male/female differences in the brain mean for changes in memory, and neurodegenerative diseases such as AD?

ADRD is of special importance to women, who make up two out of every three current patients (5). There is controversy over whether the male/female disparity in AD/D remains after controlling for women's longer lifespan (6), but closer examination is needed. Studies are accumulating that show a distinct male/female difference in the onset and course of AD.

- A study of Alzheimer's brain pathology reported male/female differences. Women had more global AD pathology than men due primarily to more neurofibrillary tangles. Each additional unit of AD pathology was associated with a nearly 3-fold increase in the odds of clinical AD in men, compared with a more than 20-fold increase in women (7).

- Similarly, the degree to which AD pathology translated into clinical symptoms was strongly dependent on male/female differences, with women more likely to have a diagnosis of AD, while men were more resistant to AD clinical symptoms in the face of the same degree of pathology. These data might suggest that the same degree of cognitive impairment is associated with greater structural damage in men compared with women (8).

- In the Alzheimer's Disease Neuroimaging Initiative (ADNI), patients were grouped into clinical categories - probable AD, amnestic mild cognitive impairment (aMCI) and healthy controls. In assessing grey matter atrophy, men and women in the AD and aMCI groups showed different patterns of decline over time (9). In another ADNI study of brain atrophy rates, statistical maps revealed significant age and male/female differences. Rates of brain atrophy were about 1%-1.5% faster in women than men (10).

- The Mayo Clinic Study of Aging reported that incidence rates for MCI were higher in men than women, and these investigators suggested that risk factors for MCI should be investigated separately in men and women (11).

- The Australian Imaging Biomarker Lifestyle (AIBL) study of aging reported that increased β-amyloid was related to worse episodic memory and visuospatial performance in females, but not in males (12).

- Last but not least, a strong risk factor in Alzheimer's is Apo e4. Female carriers of APOE ε4 have significantly more ADRD brain atrophy and memory disruption than men (13).

- Additionally, differential risk for AD was associated with estrogen receptor (ER)α and ERβ genotypes, as ERs co-localize with APOE ε4 genes and regulate their expression and co-localize with growth factors in memory circuitry regions (14, 15, 16).

AD Science

From 2000 to 2010, Alzheimer's deaths rose 68%. In addition to the enormous physical and emotional burden on patients, families and caregivers, the disease is also costly. Alzheimer's and other forms of dementia in the U.S. cost up to $215 billion annually, according to a new RAND Corporation study funded by the NIH National Institute on Aging and published in the *New England Journal of Medicine*. Around 70% of the cost of care—or $142 billion—is paid by Medicare and Medicaid. By 2050, the costs to Medicare and Medicaid are expected to increase more than 500%. In addition, this year more than 15 million Americans, mostly women, will provide unpaid care for Alzheimer's patients valued at more than $216 billion.

As more than 10,000 baby boomers (Boomers) turn 65 daily, their risk doubles every five years. It is estimated that by 2050, 11-16 million Boomers will be affected by ADRD; half the population over 85 will be ravaged by this disease. ADRD contributes to the staggering rise in health care costs, and the cost is not just monetary, as ADRD patients require full-time 24/7 care (17).

There is no cure for AD and existing treatments can only offer a brief respite from some of the symptoms, in some people. Clinical trials of new therapies in Alzheimer's dementia patients have been disappointing, so there has been a paradigm shift to look earlier in the disease process, including populations with Mild Cognitive Impairment (MCI) due to Alzheimer's (18, 19, 20) at which earlier stage, prior to severe neuronal damage, potential treatments might be more effective.

The term, "mild cognitive impairment" (MCI), due to AD refers to the symptomatic predementia phase with biomarkers consistent with AD, where the degree of cognitive impairment is not normal for age and not due to other conditions. The MCI stage is defined by evidence of lower performance in one or more cognitive domains. Additional criteria are biomarkers reflecting Aβ deposition, tau deposition, or signs of neuronal injury. Markers of Aβ include cerebrospinal fluid (CSF) measures of lower $A\beta_{42}$ levels and positron-emission tomography (PET) evidence of Aβ deposition. Tau markers include CSF measures of increased total tau or phosphorylated-tau (p-tau). Low CSF $A\beta_{42}$ and elevated CSF tau provide a high likelihood of progression to AD in patients with MCI. Other biomarkers of neuronal injury such as hippocampal atrophy and temporoparietal hypometabolism have all been shown to predict progression of MCI to dementia. Findings reflecting both Aβ accumulation and neuronal injury together would confer the highest likelihood that the diagnosis is MCI due to AD. (21)

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