Sex and Gender Differences in Alzheimer’s Disease: Recommendations for Future Research

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Abstract

Alzheimer’s disease (AD) disproportionately affects women in both prevalence and severity; however, the biologic mechanisms underlying these sex differences are not fully understood. Sex differences in the brain, such as in brain anatomy, age-related declines in brain volume, and brain glucose metabolism, have been documented and may be important in understanding AD etiology. The full impact of sex as a basic biologic variable on this neurodegenerative disease remains elusive. To address the evidence for sex differences in AD, the Society for Women’s Health Research (SWHR) convened an interdisciplinary roundtable of experts from academia, clinical medicine, industry, and the government to discuss the state-of-the-science in sex and gender differences in AD. Roundtable participants were asked to address gaps in our knowledge and identify specific sex-based research questions for future areas of study.

Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive deficits, and behavioral changes. The disease weaves an insidious path of destruction in the regions of the brain responsible for memory, learning, and higher executive functioning. Although AD was first identified over 100 years ago, little is known about the physiologic changes that trigger the disease, and current available treatments are unable to slow or reverse the damage.

There are an estimated 5.4 million Americans with AD and related dementias, and AD accounts for 60%–80% percent of all dementias. It is the sixth leading cause of death in the United States and the fifth leading cause of death of Americans ≥65. In the United States, the estimate for the number of women affected with the disease who are ≥65 years is 3.4 million compared to 1.8 million men ≥65; that is, almost two thirds of Americans with AD are women. By the year 2050, the number of Americans ≥65 affected by AD is expected to quadruple to 21 million, and correspondingly, 11–16 million people will be affected with AD if no medical breakthroughs are developed to stem the tide.

Women not only are disproportionately affected by the disease itself but also are often primary caretakers of family members affected by AD. Seventy percent of caregivers of people with AD and dementia are women,1 and reports indicate that 65% of caregivers suffer from depression.2 Currently, U.S. families and taxpayers spend almost $200 billion per year caring for those with AD.3 On a global scale, the cost of dementia is estimated at a staggering $604 billion.4

AD is characterized by an accumulation of two abnormally folded proteins in the brain, β amyloid (Aβ) and tau. Aβ is a fragment from a larger protein called amyloid precursor protein (APP), which is important for neuronal growth, survival, and postinjury repair. In AD, APP is divided into smaller Aβ fragments through an unknown process. Aβ accumulation causes formation of plaques that are deposited in the extracellular spaces (outside neurons), disrupting nerve-to-nerve communications and causing swelling of the fibers and other morphologic changes. Tau is a protein that normally functions to bind and stabilize components of the neurons of the brain. In AD, tau accumulation or aggregation forms neurofibrillary tangles that disrupt important intracellular signaling. It is these two processes, accumulation of plaques and formation of tangles, that cause the loss of synaptic integrity and selective neuronal cell death, which contribute to disease progression.5 Brains of patients with advanced AD show dramatic shrinkage from cell loss and debris from dead and dying neurons.

Studies of families with early onset AD (before the age of 65) and in Down syndrome patients (trisomy for chromosome 21), who invariably develop AD neuropathology by age 35, led to identification of the first gene associated with AD on chromosome 21. APP was identified with mutations that caused accumulation of Aβ in the brains of patients and...
affected family members. Rare dominant mutations in other genes (presenilin-1 and presenilin-2) have also been identified and are associated with early onset disease (30–65 years). A common polymorphism that confers risk, the APOE-4 genotype or allele, increases the chance of developing the disease over the other forms (APOE-2 or APOE-3). Although the APOE-4 allele contributes to 40%–50% of the genetic basis for late onset AD, it is responsible for only 10%–20% of cases. This means that ≥80% of AD cases are considered sporadic; that is, they derive from an unknown cause. Although tremendous strides have been made in the molecular and genetic pathogenesis of AD in the past 20 or 30 years, there is still much that is unknown, and little research has been conducted to understand and clarify the role of sex and gender in the onset, severity, and progression of AD.

Age and gender are the predominant risk factors for AD. In studies in both the United States and abroad, age appears to consistently predict AD across studies, but gender results are inconsistent. Speculation continues that the gender effect on disease prevalence is because women live longer. Because women survive to later ages than men, it is impossible to know if men who died would ever have developed AD at the same rate as that of women. Other risk factors include family history of AD, low number of years of education, APOE genotype, and head injury with loss of consciousness.

Sex differences in AD severity have been found, especially with regard to dementia and cognition. Cognitive test performance differences have been documented in healthy men and women as well as in patients with dementia and AD. One study demonstrated relatively equal scores on naming and fluency tests in patients with dementia, but women with AD had significantly greater impairment. Another study compared global cognitive function (last evaluation before death) to specific measures of plaque and tangle pathology derived from brain autopsy. AD pathology was more likely to manifest as dementia in women than in men, and for each additional unit of AD pathology, women had a nearly 3-fold increase in the odds of having been diagnosed with AD. Further studies are needed to correlate diagnosis and AD pathology to understand why women bear the burden of AD prevalence.

AD pathogenesis may also be influenced by metabolic changes induced by sex hormones. Estrogen is known to be protective in the brain, and loss of the hormone during menopause may be responsible for deficits in brain metabolism, which lead to AD. Male and female brains react very differently to testosterone and estradiol despite the fact that both sexes have receptors for each hormone. Both sexes can synthesize estradiol in neurons, but synaptic response in different brain regions appears to be highly sexually dimorphic. Understanding AD pathogenesis demands broad knowledge of the complex interplay among genetic, hormonal, and environmental influences. The role of sex and gender differences in the onset and course of AD remains ill-defined and demands further attention.

The Society for Women’s Health Research (SWHR) recently directed its focus on sex and gender disparities in AD. SWHR is a nonprofit organization located in Washington, DC, dedicated to building research capacity to focus on biologic differences between males and females and the critical impact of sex-based and gender-based differences in disease. SWHR convened a group of nationally recognized thought leaders for a roundtable discussion on sex differences in AD, with a specific focus on women. Before the meeting, roundtable participants were grouped into four categories based on their expertise (clinical, basic science, industry, psychosocial) and were tasked to examine their own research, with a critical eye toward areas where sex and gender differences could be identified and explored.

The SWHR Expert Roundtable on Alzheimer’s Disease in Women met in Washington, DC, on October 28, 2011. SWHR moderated the discussions and challenged the group to consider and articulate their ideas for the highest priorities for sex-based Alzheimer’s disease research. At the meeting, leaders of each of the four groups presented data, discussed gaps in knowledge, and presented concrete questions for future research. The overarching framework or theme was: How can sex and gender differences research impact our understanding of Alzheimer’s disease? This report sheds some light on this theme and highlights gaps in the form of research questions (Tables 1, 2, and 3) and recommendations (Table 4) for future areas of focus.

### Clinical Research Group

The clinical group discussed ongoing clinical trials, biomarkers, menopausal hormone use, comorbidities, and the fact that women have more autoimmune diseases, which along with systemic inflammation, confers risk for AD. Dozens of phase 3 clinical trials are in progress, including those that use intravenous immunoglobulin, semagacestat, solanezumab, bapineuzamab, raloxifene, vitamins D3 and E, thalidomide, and Huperzine. At the time of this writing, only five drugs (memantine, galantamine, rivastigmine, tacrine and donepezil) have received Food and Drug Administration (FDA) approval for AD. Tacrine is rarely prescribed today due to side effects related to liver damage. Biomarkers for detection of early disease are enormously important and include detecting levels of Aβ and tau in the cerebrospinal fluid, magnetic resonance imaging (MRI), functional MRI and position emission tomography (PET) scan imaging, and tests for cognitive performance. Recent studies on possible risk factors for AD, alzheimer’s disease.

### Table 1. Proposed Clinical Research Questions for Study of Sex Differences in Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Description</th>
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<tbody>
<tr>
<td>Are there sex differences in the incidence of AD?</td>
<td>How do sex differences manifest across the lifespan?</td>
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<tr>
<td>Are there sex differences in changes in incidence of AD over time?</td>
<td>How do sex differences change over time?</td>
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<tr>
<td>Are there sex-linked risk factors for AD?</td>
<td>How do sex differences affect genetic risk factors?</td>
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<tr>
<td>How does sex modify the effects of genetic risk factors in AD?</td>
<td>How do sex differences modify the effects of genetic risk factors?</td>
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<tr>
<td>Do sex and gender differences affect risk, rate of progression or response to treatment?</td>
<td>How do sex differences affect treatment outcomes?</td>
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<tr>
<td>Can changes in gynecologic practices contribute to the prevention of dementia?</td>
<td>How do sex differences affect prevention strategies?</td>
</tr>
<tr>
<td>Is there a clinical phenotype for women who would most benefit from hormone therapy?</td>
<td>How do sex differences affect hormone therapy?</td>
</tr>
<tr>
<td>What type and regimen of progesterone can symptomatic midlife women take and have at least cognitively neutral effects?</td>
<td>How do sex differences affect hormone therapy?</td>
</tr>
<tr>
<td>How can we improve the translation of basic science findings to clinical research and applications?</td>
<td>How do sex differences affect translation of basic science findings?</td>
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</tbody>
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### Table 4. Recommendations for Future Areas of Focus

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
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<tr>
<td>Strengthen evidence for sex and gender differences</td>
<td>How do sex and gender differences impact evidence?</td>
</tr>
<tr>
<td>Investigate sex and gender differences in biomarkers</td>
<td>How do sex and gender differences impact biomarkers?</td>
</tr>
<tr>
<td>Develop sex and gender differences in treatment outcomes</td>
<td>How do sex and gender differences impact treatment outcomes?</td>
</tr>
<tr>
<td>Explore sex and gender differences in comorbidities</td>
<td>How do sex and gender differences impact comorbidities?</td>
</tr>
<tr>
<td>Examine sex and gender differences in lifestyle factors</td>
<td>How do sex and gender differences impact lifestyle factors?</td>
</tr>
<tr>
<td>Identify sex and gender differences in genetic factors</td>
<td>How do sex and gender differences impact genetic factors?</td>
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show that cardiorespiratory fitness is associated (negatively) with dementia mortality for both men and women, but women benefit less than men.20 American women on average get less exercise than men per week, and this may influence their risk for AD.21 Women have higher rates of depression and anxiety, and these are emerging as risk factors for AD.22

The role of hormone replacement therapy (HRT) is still a confused issue, and roundtable experts discussed research that supports improved cognitive function with HRT when given at early but not late stages of the menopausal period, consistent with studies that claim a window of opportunity.23–26 The clinical research group agreed that the main gaps in knowledge pertain to both hormonal influence and bioenergetic aging. These gaps in knowledge are addressed as clinical questions in Table 1.

### Basic Science Research Group

The basic science working group focused on three topics that pertain to sex differences: metabolism, physiology of hormonal regulation, and AD genetics, all relevant to AD pathology.

Brain hypometabolism is one of the earliest hallmarks of AD. The brains of AD patients show a deficit of mitochondrial function and a form of reduced metabolism, changes that apparently predate the development of AD. In normal individuals with a maternal history of AD, there are significant reductions in brain glucose metabolism.27 This may be important, as mitochondrial DNA is inherited through the maternal line, and risk to offspring of AD patients may be transmitted through mitochondrial rather than nuclear DNA. The roundtable experts suggested that further research on brain hypometabolism could lead to personalized interventions to prevent, delay, or treat bioenergetic deficits in at-risk populations (Table 2A).

AD pathogenesis in women may be influenced by metabolic changes induced by gonadal hormones, such as estrogen, which is known to have a protective effect on the brain, and loss of estrogen during menopause could, in part, lead to the deficits seen in brain metabolism in mild cognitive injury (MCI) and AD. Transgenic animal studies have provided evidence that both male and female gonadal hormones regulate AD pathogenesis.28–30 Several studies in mice support...
higher risk for AD in females mediated by Aβ or APP or both, but the key entity is unclear. Increased AD risk in females may arise from a manifestation of:

- Increased pathology
- Increased synaptic degeneration and cognitive impairment
- Altered inflammatory response

There is evidence for varied effects of sex hormones on tau, which helps to regulate synaptic plasticity. Mutations in tau can cause inherited forms of dementia and form pathologic tangles in the AD brain. Animal models have shown that either female mice develop more tangles or male mice possess greater protection against tangle formation. Despite these discrepancies in animals, the roundtable scientists pointed out that significant sex differences in tau pathology in humans with AD have not been documented. Clearly, tau pathology deserves more attention with respect to sex differences and hormones to elucidate the mechanisms surrounding its toxicity (Table 2B).

Roundtable experts discussed the influence of genetics in AD and clarified that many minor genetic factors combine to affect brain development and aging over time. Recent genome-wide association studies have identified a broad range of genetic mutations associated with AD. In 2007, meta-analyses of the AlzGene database maintained by the Alzheimer’s Research Forum reported 2920 polymorphisms in 666 genes discovered in 1382 studies. Although a small minority of patients develop AD based solely on inherited genetic mutations, examination of genes and epigenetic factors is an enormously important area of research for unraveling the complex etiologic factors underlying this disease. Important gaps for genetic studies in understanding sex differences in AD are discussed in Table 2C.

**Psychosocial Research Group**

Our roundtable psychosocial experts involved with caregivers indicated that approximately 15 million people in America are unpaid caregivers for family and friends with AD. The majority of these people (>70%) are women, and the burden is substantial; typically, between 15% and 40% of caregivers provide >40 hours a week. Gender differences in spousal care are highly prevalent for patients with dementia, more so than with other illnesses. Husbands with AD and related dementias (ADRD) receive an average of 31% more hours of spousal care than ADRD wives do from their husbands. Wives also continue to provide care
longer and at greater levels of disability than husbands and with less help from adult children.\textsuperscript{34,35} Adult children, usually daughters, intervene more to help husbands caring for ADRD wives, particularly as needs increase and the disease progresses.\textsuperscript{36}

Women also have lower levels of social support and poorer psychologic and physical health. Gender identity influences an individual’s interpretation of caregiving and receiving.\textsuperscript{37} Men with traditional beliefs about masculinity are less likely to report feeling burdened and more likely to articulate the positive aspects of being a spousal caregiver; they are less likely to seek help.\textsuperscript{37,38}

Family caregivers for ADRD patients suffer greater stress than other types of caregivers, which manifests both emotionally and physiologically. Compared to other caregivers, they have high levels of stress hormones, reduced immune function, slower wound healing, and onset of both hyper-tension and coronary heart disease. At least one third of family caregivers have symptoms of depression. Because AD typically lasts for 5–15 years and the nature of symptoms is so variable, a caregiver must learn to adapt continually to the patient’s needs. The inevitable increase in cognitive and functional impairments leaves the patient completely dependent on the caregiver. The research questions raised by the psychosocial experts are presented in Table 3.

Conclusions

SWHR challenged the Expert Roundtable on Alzheimer’s Disease in Women to provide recommendations in the clinical, basic, and psychosocial studies in the incidence of sex differences in AD (Table 4). They were further asked to reach a consensus on this set of recommendations, which encompass seven overarching themes.

- Examine incidence of AD by sex
- Analyze sex-based differences systematically and comparatively
- Raise awareness to incorporate sex and gender into experimental design
- Define standards for biomarkers and diagnosis; determine how biomarkers relate to disease burden and risk for AD
- Examine HRT in the context of AD
- Integrate sex differences in AD drug discovery
- Consider sex and gender differences for the family caregiver

There is much to be explored in the realm of sex and gender differences in AD, but a wealth of data ready for meta-analysis is being accumulated. Sex differences research in AD is aimed toward improving early diagnosis, better quality of life, and safer, more effective treatments. Sex differences in AD are important, and every study should stratify and report data by sex and carefully consider the ramifications for sex differences across all aspects of the disease. Further, treatments for AD must account for sex differences and the gender-specific needs of our patients. Finally, we need to conduct more research on ways to better meet the needs of people with this dreadful disease so that both the caregivers and the patients see an improvement in their quality and length of life.

Participant List: SWHR Expert Roundtable on Alzheimer’s Disease in Women

Clinical Research Group

Victor Henderson, M.D., M.S., Stanford University
Pauline Maki, Ph.D., University of Illinois, Chicago
Walter Rocca, M.D., M.P.H., Mayo Clinic
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John Morrison, Ph.D., Mount Sinai
Steven Snyder, Ph.D., NIMH, N.I.H.
Rudy Tanzi, Ph.D., Harvard University

Psychosocial (Caregivers) Research Group

Mary Mittelman, DrPH, New York University
Darby Morhardt, M.S.W., LCSW, Northwestern University

Industry Scientists

Rachel Schindler, M.D., Pfizer, Inc.
David Biondi, D.O., Janssen Scientific

Note: Lester Binder, Ph.D., Northwestern University, and Samuel Gandy, M.D., Ph.D., Mount Sinai, participated in planning sessions but were unable to attend the roundtable.

Disclosure Statement

The authors have no conflicts of interest to report.

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