Sexual differences regarding Alzheimer’s disease: a narrative review

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Background. Actually, there are about 5.2 million people with Alzheimer’s dementia (AD) in the USA, 3.3 million are women and 1.9 million are men.

Objective. We will find out the status on the Alzheimer disease in relation to the brain structure, diagnosis, symptoms and therapy by gender.

Methods. We analyzed, in this narrative review, the literature between 1989-2019 published on the Pubmed about Alzheimer disease and gender. The keywords were: Alzheimer disease and sex differences.

Conclusions. Women over 80 years have a higher incidence of AD than men. Women have a faster age-related decline and are more likely to respond to donepezil and rivastigmina leading to less cognitive decline. At more advanced ages, women incurred greater costs than men of the same age. Woman gender could be a risk factor for evolution of AD. We will emphasize the importance of considering sex as a biological variable in the design of preclinical and clinical studies that investigate underlying pathologies or response to pharmacological interventions in AD.

Key words: Alzheimer disease, gender differences, dementia, women, gender related

EPIDEMIOLOGY

Alzheimer’s disease (AD) is the most common type of dementia and comprises about 60-70% of all dementia cases. Women are at the epicenter of the AD. In fact a woman’s estimated lifetime risk for developing AD is 1 in 6 and almost two-thirds of Americans with AD are women. Actually, there are about 5.2 million people with AD in the USA. In particular, 3.3 million are women and 1.9 million are men (Fig. 1). Many European and Asian studies showed that the incidence of AD increases with age and it is similar in men and women until 78-80 years. Up to age of 80 years, women have a higher incidence of AD than men. These differences across Europe, Asia and North America may be due to social, cultural and historical events.

SEX DIFFERENCES AND RISK FACTOR

Sex differences in incidence of AD are due to differences in brain structure between men and women. Head size and cerebral brain volume is
10% larger in men than women. Also, women have a higher percentage of grey matter and hippocampus, whereas men have a higher percentage of white matter, amygdala and thalamus (Fig. 2). These sex differences contribute to performance differences. In particular, men perform better on visually oriented tasks, while women perform better on verbal memory.

**ε4 allele of the Apo lipoprotein E (APO E) gene**

The ε4 allele of the Apo lipoprotein E (APO E) gene is the best-known risk factor for AD. The effect of the ε4 genotype is more pronounced in women than in men. In fact, an autopsy study found that amyloid plaque and neurofibrillary tangle pathology was greatest among women who were ε4 carriers. However, the risk of AD is higher in women with homozygous ε4 carriers compared with men with homozygous ε4 carriers. Different studies reported that women with one ε4 allele had about four-fold risk of AD, whereas men with one ε4 allele had a little increase risk. Many studies reported the associations between ApoE and delusion, aggression, anxiety, apathy, and depression in AD. Noteworthy, the effect of ApoE ε4 on AD are more evident in women than in men. A study pointed out that ApoE ε4 status regulated the effects of sex hormones on neuropsychiatric symptoms of AD in women patients but not in men.

**Hormone replacement therapy (HRT) and AD**

Observational studies showed that the use of hormone replacement therapy (HRT) reduces the risk of AD when it is initiated around the time of menopause. Women who initiated HRT within 5 years of menopause had a 30% lower risk of AD compared to women who did not use HRT.

**Exercises and AD**

Some studies suggest that exercise lowers the risk of AD more in women than men. In particular, physical activity in the teenager was associated with the greatest reduction in risk of AD.
SEX DIFFERENCES IN SYMPTOMS

Several studies underlined that women show more evident language, semantic and orientation deficits, but methodological limitations might be responsible for this finding. Also, there is uncertainty on the validity of results reporting a more rapid cognitive decline in women. Women show a wider spectrum of dementia-related behavioral symptoms such as depression, while aggression is more frequent in men. Women seem to be more susceptible for pathological lesions while men have greater cognitive reserve. Neuropsychiatric symptoms affect most of patients with AD. Some authors suggested that patients with AD were more frequently to show apathy and anxiety, while delusion was more common in female. It was reported that the atrophy of hippocampal region was associated with agitation and aggression in AD. Interestingly, some studies demonstrated that women with Mild Cognitive Impairment (MCI) and AD and ApoE ε4 carrier, had smaller hippocampal volumes than men. However, it has been reported that pre-morbid depressive symptoms, significantly increased risk for dementia, particularly AD in men but not in women. However, the underlying pathophysiological mechanisms of neuropsychiatric symptoms of AD are still not completely clear.

SEX DIFFERENCES IN DIAGNOSIS

Dementia diagnosis differs in men and women and depends on age and severity of the disease. Older age is a risk factor in specific subgroups and it is associated with greater declines in global cognition. In particular, Cherbuin et al. reported an association between mean arterial blood pressure and regional gray matter, both in men and women. Other authors reported an association between diastolic blood pressure and regional gray matter in men only. Women have a higher risk of developing AD than age-matched men, and showed faster age-related decline and greater deterioration of cognition compared to elderly male. However, a significant interaction by gender was found in patients with subjective memory complaints (SMC). Peres et al. showed that Instrumental Activities of Daily Living (IADL)-restriction increases the risk of dementia in men. The authors reported that, in men, IADL-restriction is only associated with increased risk of dementia at short-term, but not at longer term. In women, SMC is significantly associated with greater risk of dementia even at longer term. Another study demonstrated sex differences in cognitive impairments. In particular, cognitive impairment in women is associated with greater declines in fluency capacity, while in men it is associated with significant declines in visual-spatial ability. In relation to the Mini Mental State Examination (MMSE) score, at initial diagnosis, it has been reported that it dropped significantly with increasing age. Gender and place of residence are significantly related to the MMSE score. In particular, it has been reported that women and institutionalized patients have lower MMSE scores under the age of 90 years and at all educational levels. In women, delirium severity was related to dementia severity. For men, unlike for women, delirium severity was greater in those with less educational level. Differences were reported in relation to gender and race. African American women reported greater difficulty with all Basic activities of Daily Living (BADLs) and IADLs with the exception of dressing and using the telephone. In comparison to men, non-Hispanic White women, also reported significantly increased difficulty with transfers, revealing a sex disparity in this mobility-related daily activity. African American men and non-Hispanic White men demonstrated an equivalent prevalence of difficulty for all BADL tasks. However, for all IADLs African American men reported greater difficulty compared to non-Hispanic White men.

SEX DIFFERENCES IN THERAPY

Gender differences in symptom profile, living conditions, coping style and response might affect the outcome of psychosocial interventions (PSIs). Caregiver interventions found gender differences in PSIs outcome. Women improved significantly with psychosocial interventions in relation to behavioral and psychological problems (Neuropsychiatric Inventory scores) at the 12-month. In studies investigating music therapy, to be male is, a predictor of poorer outcome in terms of greater physical aggression. Furthermore, gender may influence the response to acetyl cholinesterase inhibitors (AChEIs). Indeed, women are more likely to respond to donepezil and rivastigmina leading to less cognitive decline. However, sedative-hypnotics are over-prescribed to women. To this regard, women are at a greater risk for side effects. In particular, it has been reported that bradycardia, from cholinesterase inhibitors, may affect more women, while men will experience more emergency hospitalizations and death after prescription of an antipsychotic. A study reported that gender differences in neuropsychiatric symptoms could influence the decision of treatment, and male patients could be more likely to receive antipsychotic medica-
DEMENTIA AND HEALTH POLICY

Differences are observed in relation to costs of dementia. In particular, it has been observed that about two-thirds of the additional expenditure for dementia patients occurred in the long-term care. Long-term care spending increases in older age. In particular, women accounted for significantly lower health and significantly higher long-term care expenditures. Thus, at more advanced ages, women incurred greater costs than men of the same age. These data represented a clear gender difference in the length of stay. The length of stay of women is longer than that of men. In particular, older age is predictor of the length of stay in women.

KEY MESSAGE

- Many European and Asian studies showed that the incidence of AD increases with age and it is similar in men and women until 78-80 years.
- Dementia diagnosis differs in men and women and depends on age and severity of the disease.
- Women have a higher risk of developing AD than age-matched men, and showed faster age-related decline and greater deterioration of cognition than elderly male.
- Furthermore, gender may influence the response to acetyl cholinesterase inhibitors (AChEIs). Indeed, women are more likely to respond to donepezil and rivastigmina leading to less cognitive decline.
- Women accounted for significantly lower health and significantly higher long-term care expenditures.
- In comparison to men, women reported significantly increased difficulty with transfers and in the mobility-related daily activity. However, several studies showed that high blood pressure, poor hearing, regular exercise, normal weight and having limitations in instrumental activities of daily living, were significant predictors of cognitive impairment in women.

CONCLUSIONS

Several mechanisms have been proposed to explain gender and educational differences in dementia risk. It suggests that inborn intelligence and a mentally stimulating lifestyle, such as educational and occupational attainments, may delays cognitive decline or dementia onset by increasing an individual’s brain reserve. In conclusion, gender could be a risk factor for evolution of AD. Future clinical trials should investigate the possible mediation effects of various biological factors (e.g. genetics, hormones, brain networks) in relation to the observed association and more studies need to assess gender differences rather than just adjusting for gender in analyses. Given the double aging of our society and the worldwide increase in sedentary lifestyle behavior, policy makers, insurance companies, and public health campaigns should place more emphasis on brain-healthy lifestyle changes in middle aged and younger subjects to promote optimal brain ageing and prevention of dementia in the long-term.

References

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