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Gender differences in cognitive decline and Alzheimer's disease

Carlo Gabelli[1], Alessandra Codemo[1]

Summary. Sex and gender impact on human brain biology throughout individual lifetime, influencing male and female cognition in a differential mode. Women are exposed to a higher risk of Alzheimer's disease and AD prevalence is higher in females, particularly among older age groups. The negative effect of APOE ε4 allele and lower education may explain at least part of the gender disproportion. However, the biological modifications underlying these observations remain poorly understood. Menopause is associated with increased AD risk and a well-timed hormonal replacement therapy might be considered, especially in young women undergoing bilateral oophorectomy. In addition, cardiovascular risk factors such as type 2 diabetes and hypertension show an increasing prevalence in the female sex and play a significant role in AD risk. Taking into account the sex/gender issue in neurocognitive research, it is critical to set effective strategies against AD.

Key words. Gender, cognitive decline, Alzheimer's disease.

Le differenze di genere nel declino cognitivo e nella malattia di Alzheimer

Riassunto. Le differenze di sesso e di genere, intese come effetti culturali e sociali, influenzano lo sviluppo e la biologia del sistema nervoso centrale nel corso di tutta l'esistenza dell'individuo. Ne consegue che anche le funzioni cognitive presentano delle peculiarità di genere e sono diversamente influenzate dai processi patologici che portano alla demenza. La malattia di Alzheimer è la principale forma di demenza e, a causa dell'invecchiamento globale della popolazione, è destinata a una rapida crescita. Le donne sono esposte nell'arco della vita a un rischio di Alzheimer quasi doppio rispetto agli uomini e la prevalenza di malattia è nettamente maggiore, specie nelle fasce di età più avanzata. Anche se la maggior mortalità maschile può spiegare in parte queste differenze, è chiaro che altri fattori entrano in gioco. Ad esempio, l'effetto negativo dell'allele ε4 di APOE e un basso grado di scolarizzazione contribuiscono allo squilibrio tra i sessi. La menopausa si associa a un aumentato rischio di malattia di Alzheimer e una terapia ormonale sostitutiva effettuata nel tempo più opportuno può avere un ruolo positivo nel ridurre il rischio di malattia. Anche i fattori di rischio cardiovascolari giocano un ruolo nell'insorgenza della malattia di Alzheimer. Il diabete tipo 2 e l'ipertensione mostrano un preoccupante incremento di prevalenza tra le donne a livello globale. Il sesso femminile è maggiormente colpito dalla malattia di Alzheimer sotto diversi punti di vista: epidemiologico, biologico e sociale, ma la ricerca ha finora considerato questi aspetti con insufficiente attenzione. Gli aspetti legati al genere sono invece fondamentali per la ricerca futura e per formulare strategie di cura efficaci.

Parole chiave. Genere, declino cognitivo, malattia di Alzheimer.

Introduction

Dementia, or major neurocognitive disorder as it is termed by DMS-5[1], is an umbrella definition comprising different conditions causing cognitive disability: Alzheimer's disease, Vascular dementia, Lewy Body Disease, Frontal Lobar Degeneration, post-traumatic dementia and others. Since Alzheimer's disease (AD) is the most common form of dementia and is strongly associated with aging, it has became the focus for research in the field.

With increasingly aging populations, AD has grown into a major global public health concern due to the rapid rise of its prevalence and its economic impact on society. Dementia cases across the world will triple by 2050 and 1 in 85 people will be affected by Alzheimer's disease[2]. Given that the total cost of dementia is about 1% of the global GDP[3], the issue is no longer only a medical problem and has gained political attention.

Women carry a higher AD burden: they are disproportionally affected by AD and are at higher risk of developing the disease[4]. Gender differences in rate of progression after diagnosis and response to therapy have also been reported. Finally, most caregivers are female family members[2].

While substantial progress has been made towards understanding the biological basis of neurodegeneration, the question of gender's impact on AD has not been completely understood. The development and functioning of the central nervous system is strongly influenced by sex and gender. Apolipoprotein E gene (APOE) polymorphism, estrogen exposure and education are important modulators of beta amyloid deposition and cognitive decline. Thus far, being male or female is not considered an important characteristic in clinical practice and research.

1. Centro Regionale per lo studio e la cura dell'Invecchiamento Cerebrale (CRIC), Dipartimento di Medicina, Azienda Ospedaliera Universitaria di Padova, Padua, Italy.

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In this review, we will focus on the recent evidence that women are more at risk of AD, highlighting relevant biological and environmental factors that explain difference between sexes with regard to cognitive function and age-associated decline.

Cognitive function, age and sex

The brain is strongly influenced by sex (biological differences due to chromosomes XX and XY, gonadal hormones) and gender (intended as cultural and psychosocial differences).

It is hardly surprising that an increasing number of publications show the biological basis of a phenomenon that can be experienced everyday: men and women behave differently.

Sex differences in cognitive function and brain structure in later life have been demonstrated by magnetic resonance imaging (MRI) in human studies. Men show larger amygdala and thalamus volumes whereas the hippocampus is larger in females[5-7]. More recently Ingalhalikar et al.[8] demonstrated a striking difference in the human structural connectome of the two sexes (Figure 1). They studied a large population of 949 youths (8-22 y, 428 males and 521 females) using diffusion-based MRI. The results establish that male brains are optimized for intra-hemispheric communication and female brains for inter-hemispheric communication. The developmental trajectories of males and females separate at a young age, demonstrating wide differences during adolescence and adulthood. The observations suggest that male brains are structured to facilitate connectivity between perception and coordinated action, whereas female brains are designed to facilitate communication between analytical and intuitive processing modes.

Different performances have been observed between sexes when undertaking a number of common tasks, in literature relating to both humans and animals. For example, adult men perform better with regard to spatial memory, while women excel at verbal skills and object location[9-10]. Cognitive functions in women may depend on hormonal status, women in high estradiol phases of the menstrual cycle have better verbal fluency than those in low estradiol phases, and natural cycling women have better verbal fluency than women using oral contraceptives[11-12].

On the other hand, these differences are shown to be dependent on environmental factors. In a large study involving 14 European countries and 38000 people aged >50 years it was demonstrated that improved living conditions and less gender-restricted educational opportunities are associated with increased gender differences, favoring women in some cognitive functions (episodic memory) and decreasing or eliminating differences in other cognitive abilities[13].

Cognitive abilities tend to decrease with age. In

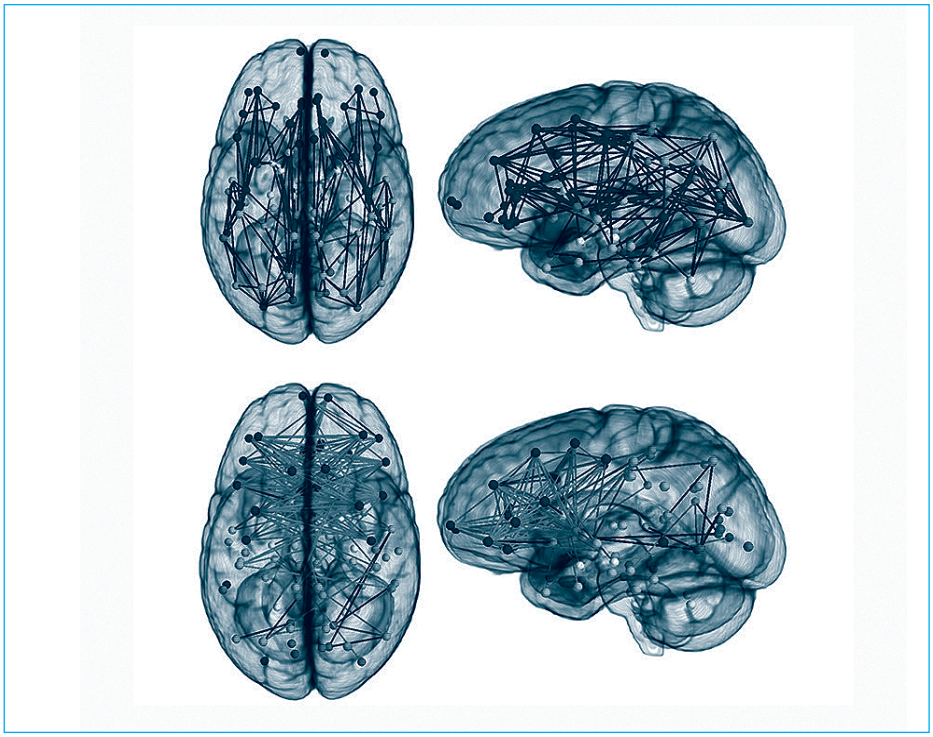

Figure 1. Sex differences in the structural connectome of the human brain: upper panel males, lower panel females. Modified from Ingalhalikar et al, 2014[8].

a longitudinal study, Yamada et al.[14] examined 1558 dementia-free subjects aged 60 to 80 years in 1992, following subjects without dementia occurrence until 2011. Using the Cognitive Ability Screening Instrument, they found that cognitive decline became more rapid with increasing age. Education level affected cognitive function level, but did not affect cognitive decline. Sex did not modify the degree of deterioration with age.

In a different cross-sectional study[15], the content of brain amyloid by PET imaging and memory were evaluated in 1246 cognitively normal participants between the ages of 30 and 95. The participants were categorized into four groups according to sex and whether or not they carried the APOE ε4 gene. Overall memory appeared to worsen in participants from the age of 30 through to their 90s. Hippocampal volume also decreased from the age of 30, with a worse decline after the age of 70. The average amount of amyloid accumulation was low until the age of 70. APOE ε4 carriers had greater average amyloid accumulation than non-carriers. Interestingly, memory performance and hippocampal volume were unaffected by apoE allele status. Overall, men had worse memory than women at 40 and lower hippocampal volume than women at 60. However, these measurements were not affected by APOE ε4 carrier status at any age. The study is limited in that it is a cross-sectional observation, so its findings cannot prove causation. Additionally, it only examined data for individuals selected to be cognitively normal, who represent a subset of the normal population.

Since diagnosis of AD and Mild Cognitive Impairment (MCI) must be anticipated at a very early phase, we need to use more and more specific and sensitive neuropsychological batteries. In light of the differences in cognitive performances between normal elderly people and AD[16] sufferers, it seems reasonable to evaluate the need to select gender specific batteries or correction methods.

Alzheimer's disease

The prevalence of AD is significantly higher in women compared to men. Recent data suggests that almost two thirds of AD sufferers are women[4]. The main risk factor for AD is age and the fact that the majority of AD patients are females is traditionally attributed to longer life expectancy.

Reported prevalence rates among different populations vary considerably[17-22]. Methodological reasons such as clinical diagnostic criteria, sampling strategies and statistical analysis can explain the differences[23]. In general, women are reported to have higher rates of AD than men, even after adjusting for survival. This is particularly true in the case of women aged over 75 years.

Incidence is a more appropriate measure of the risk of disease. However incidence rates show more conflicting results. Some studies find no difference[24-27] and others[28-31] indicate a significantly higher incident rate of AD in females, especially in the oldest age categories. Studies conducted in North America do not find much difference, whereas epidemiological research in Europe and Asia often describes significant increased incidence of AD in women. However, a large meta-analysis conducted by Gao et al.[32] shows that the risk of AD is increased 1.6 fold in women.

Longitudinal results from the Framingham study were even more convincing[33]. If the lifetime risk is considered, it shows that females are exposed to a nearly twofold greater age-specific lifetime risk (17.2 versus 9.1 at 65 years of age and 28.5 versus 10.2 at 75 years) (Figure 2).

Sex-related differences can be observed in the clinical and biological manifestation of AD. Hua et al.[34] examined 1-year atrophy rates, using 3D tensor-based MRI morphometry in 1368 MRI scans from the Alzheimer's Disease Neuroimaging Initiative (ADNI). They studied 144 subjects with AD, 338 subjects with MCI and 202 controls. They found that annual atrophy rates were faster in women by 1-1.5% and the atrophy rates correlated with amyloid beta and Tau changes in CSF and with apoE allele status. Similar results were obtained by another group[35] that studied cognitive decline and brain atrophy with MRI in 668 subjects over a 3-year period. Women showed greater atrophy rates and faster cognitive decline than men.

In a clinicopathologic longitudinal study on 141 individuals with AD, MCI or cognitive impairment, which evaluated clinical and post-mortem data, a significant correlation was found between gender and neuritic plaques and neurofibrillary tangles after controlling for age[36]. According to this study, on a global measure of AD pathology that ranged from 0 to 3, each additional unit of pathology increased the odds of clinical AD nearly 3-fold in men compared with more than 20-fold in women.

All these considerations about gender differences do not pertain to familial AD, due to mutations of APP, PSEN1 or PSEN 2 genes. A genetic background, autosomal dominant, seems to prevail over other factors[37].

Brain sex differences and hormonal effects

Both genetic (X and Y chromosomes) and hormonal effects contribute to the physiology underlying

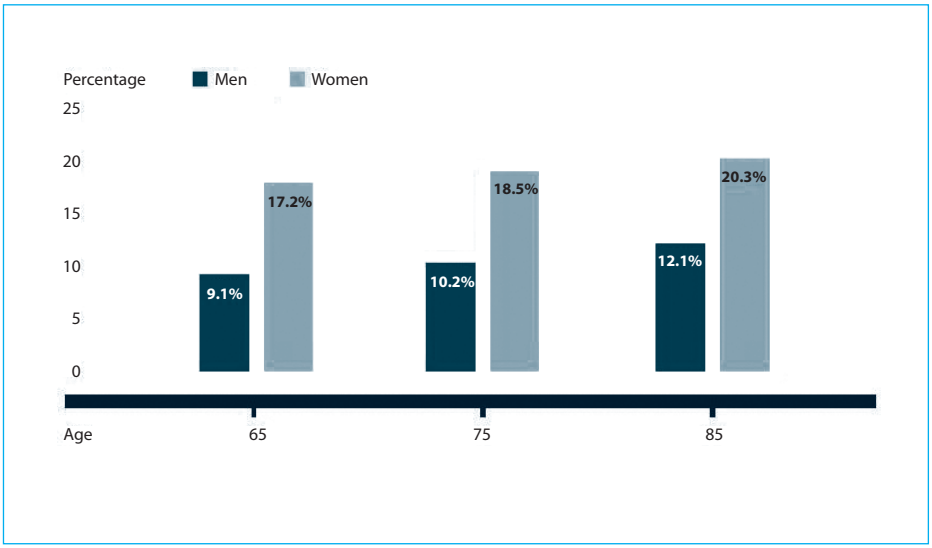

Figure 2. Framingham estimated lifetime risks for Alzheimer's disease by age and sex. Modified from Seshadri et al, 2006[33].

sexual dimorphism of the brain. Before the influence of gonadal hormones, male and female brain developing cells show specific differences in gene expression[38]. For instance, in the rat model, the Y chromosome-linked, male-determined gene Sry is specifically expressed in the *substantia nigra* that is involved in the dopaminergic expression and motor behavior control of an adult animal[39].

Sex hormones act as critical neurotrophic factors in the perinatal period and throughout the lifespan. Endogenous estrogen has been shown to be protective toward AD. It potentially reduces amyloid-beta aggregation and improves a number of neural functions, including cerebral blood flow and glucose metabolism[40-41] and synapse formation on hippocampal dendritic spines[42-43], while also increasing choline acetyltransferase activity in the basal forebrain and hippocampus[44-45]. Aging and cognitive decline are associated with a decline in gonadal hormones. In men, the reduction of testosterone is gradual while in women there is a rapid loss of estrogen after menopause.

Based on these assumptions, a large randomized trial of HRT was initiated, including several thousands of women – the Women Health Initiative Memory Study (WHIMS) – but results were quite disappointing, women older than 65 who were randomized to HRT with estrogen plus progestin showed an increased risk of MCI and AD of 37%[46] and a significant reduction in the hippocampal and frontal lobe volumes[47].

Following menopause, women experience a relatively sharp decline of the ovarian sex hormones 17-beta estradiol and progesterone. Bilateral oophorectomy prior to menopause causes an abrupt deficiency of estrogen, progesterone and testosterone and almost doubles the risk of AD[48]. Women who initiated hormone replacement therapy (HRT) just after bilateral oophorectomy and continued the treatment until the age of natural menopause did not experience an increased risk[49]. In line with these results, observational studies using HRT around the time of menopause show a reduction of risk. In the Cache County Study, women who started HRT within five years of menopause had a 30% lower risk of AD compared to women who reported no use of HRT. However, subjects who began therapy more than five years after menopause did not have a reduction in risk, and if they started HRT after 65 years of age they had an almost two-fold increased risk[50]. Similar results were obtained in the MIRAGE study and in the Northern California Kaiser Permanente study[51-52].

In light of the observational data suggesting that the initiation of estrogen in the immediate years after menopause is protective, whereas later use can increase AD risk, a "critical window" concept was postulated[53] and the results of WHIMS are hardly surprising. WHIMS' subjects were aged 65-79 years old at baseline. Thus, HRT was initiated 10-20 years after the onset of natural menopause.

Apolipoprotein E gene polymorphism

Apolipoprotein E (APOE) has important functions in the CNS, acting as a carrier of cholesterol and beta amyloid between cells and the blood brain barrier. The ε4 allele of APOE gene is the strongest known genetic risk factor for late onset AD: subjects carrying one or two ε4 alleles (about 15% of the caucasian population) are exposed to a significantly higher risk of AD[54]

and to an earlier age of onset of the disease[55]. In a longitudinal epidemiological study, the presence of a single or double ε4 allele did not confer a significantly increased risk in men (OR 1.6, 95% CI = 0.5-5.3) while in women a substantially higher risk was found (OR 7.8, 95% CI = 3.2 – 19.1)[56]. The results were confirmed in other studies and in a large meta-analysis, collecting 5930 AD cases from 40 teams[57]. Even if significant variability is observed between different ethnic groups, ε4 carrier females show a higher risk of AD compared to males. These findings may in part account for the observed disproportionate risk faced by women, as proposed by Payami et al.[58]

At the biological level, a number of negative effects of ε4 on female gender have been reported. Women with ε4 show, compared to their sexual counterparts, decreased cortical thickness, decreased hippocampal volume and functional brain connectivity, increased spinal fluid protein TAU levels[59-61]. Beta amyloid deposition and tangle pathology, evaluated in a large autopsy study, are significantly higher in ε4 women than in men[62].

More specific research is needed in order to clarify the biological cause of the increased negative effect of ε4 allele in females.

Lifestyles and cardiovascular risk factors

Specific factors related to gender identity and social roles may contribute to the risk of AD, including education, occupation, diet and exercise, smoking and drinking behaviors.

Low education and low occupational history (unskilled workers) have been consistently associated with an increased risk of AD[63-65]. Intellectual lifestyle (education, occupation and current cognitive activity) explains more than 10% of the variance in an individual's cognitive performance[66]. In other words having a higher education/occupation and greater engagement in cognitive activities provides higher reserve against the disease and results in varying cognitive aging trajectories among individuals. All these factors are tied to the concept of "cognitive reserve"[67-68]. The mechanism by which low education and occupation are thought to increase risk of AD is by lowering the cognitive reserve.

In general females have a lower cognitive reserve compared to men, mainly due to different access to education in the past century. Since women living in Europe and North America in the first part of 1900 had different opportunities regarding school and employment, gender-related differences may explain the observed geographical differences in the prevalence and incidence of AD described above.

Recent imaging studies using beta amyloid tracers (PIB) and FDG-PET have shown that subjects with higher education or occupational engagement have more pathological changes when compared to subjects with lower education at the same level of cognitive performance, in other words they have grater cognitive reserve[69-70].

Common cardiovascular risk factors such as hypertension, type 2 diabetes and obesity are associated with dementia, however they do not only contribute to cognitive decline associated with vascular impairment, but also significantly to AD.

The adverse impact of these health problems will affect women, in particular given the rise in the proportion of the >75 ys female population. The distribution and prevalence of major risk factors between the sexes and age groups have changed[71]. The prevalence of hypertension is higher in men than in women until the age of 60, but subsequently prevalence in females is greater than in men, especially of systolic hypertension[72].

There is increasing evidence that type 2 diabetes mellitus (T2DM) is a risk factor for AD and MCI[73-74], hippocampal cells in AD share metabolic features similar to T2DM[75]. Diabetes is increasing in frequency to a greater extent in women than in men[76] and produces different effects on the two sexes[77].

Physical activity has been demonstrated to have positive effects on cognition and may play a role in AD prevention[78], but global trends show a progressive reduction in movement in both sexes[79], increasing the general risk of obesity and T2DM, particularly in elderly women.

Conclusions

There has been insufficient research into understanding why MCI and AD have a different gender expression.

A large body of data indicates important biological and functional differences in the brain of males and females that can change over a lifespan depending on hormonal status and lifestyles. However, existing biomarker studies on gender differences in AD have been largely *post hoc* and exploratory in nature. Further examination of gender effects in longitudinal multicenter studies and population studies might be crucial when evaluating possible differential strategies to prevent cognitive decline, and to select and treat subjects with Alzheimer's disease before it leads to disability.

Given the need for a tailored, prompt diagnosis and intervention in AD, gender consideration has become clinically relevant.

Key messages

- Sex and gender have a fundamental role in the development and organization of brain function.
- Women are at higher risk of developing AD than men and show a higher prevalence and rate of decline.
- Estrogen status is an important factor in AD risk and can be modulated by HRT.
- APOE gene ε4 allele causes worse negative effects in women than in men.
- Better education and lifestyle improvement may change the disproportionate risk for females in the future.

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Correspondence to:
Carlo Gabelli
Centro Regionale per lo studio e la cura dell'Invecchiamento Cerebrale (CRIC),
Dipartimento di Medicina,
Azienda Ospedaliera Universitaria di Padova
Italy
email carlo.gabelli@sanita.padova.it