

## Gender and dementia

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Among the great world challenges the problem that populations, globally, are getting older is one of the most important. In 2025 subjects of 60 years and older living in Italy, Germany, Spain, Portugal and Finland will reach 35% of the total population. Women will live longer than men, but this may mean more years spent in ill health. Men have a shorter life expectancy than women do, but they will enjoy a greater proportion of their lives in good health<sup>1</sup>.

Dementia is one of the major diseases linked to aging and leading to disabilities for all the affected people. However, dementia is a syndrome encompassing hundreds of different diseases, each of them with a peculiar clinical phenotype and a specific course of duration. In the last twenty years molecular genetics has been highlighting Alzheimer's disease (AD) and fronto-temporal dementia (FTD) especially from a causative point of view through the identification of some key genes. Although mutations are rare, this type of study has given the possibility to inquire into the pathogenic mechanisms isolating pathological proteins and diseased circuits and understanding in part how, for example, AD starts in the brains<sup>2</sup>. Genetic forms of AD and FTD could be considered as models for the major, common and undetermined, sporadic forms.

Much more has been accomplished in detecting dementing illnesses from a clinical point of view, in better defining earlier diagnosis with biomarkers, and deeply studying overlapping phenotypes, their variability and course. Unfortunately, this has not corresponded to the great (and expected) advancement in the pharmacological treatments.

It is also of note that different gender issues have not permeated the dementia research world; data are scarce, frequently inferred from other researches having other aims and analyzing different contexts and different sets of populations and not specifically produced and dedicated to address those issues.

This is a major limitation that is important to overcome because just as other diseases differentially affect men and women, also the different types of dementia seem to show gender related expressions.

The ILSA study, the Italian epidemiological study conducted by CNR, has long reported a major prevalence

of AD in women and vascular dementia in males<sup>3</sup>, Lewy body disease has a great expression in the cortical brain of males<sup>4</sup> and in the same gender direction PD dementia has been signaled<sup>5</sup>.

A recent revision work<sup>6</sup>, reconfirming that AD is preferentially expressed in women and Parkinson disease, Lewy body dementia and vascular dementia are found more frequently in males, add data on frontotemporal dementia (gender differences much more debated) and on the rare Creutzfeldt-Jakob disease (CJD) on which gender analysis has never been reported.

Higher female prevalence of chromosome 9 open reading frame 72 (C9orf72) hexanucleotide repeat expansions in Amyotrophic Lateral Sclerosis (ALS), and progranulin (GRN) mutations in FTD has been found in a metanalysis analyzing 12,784 ALS patients<sup>7</sup>. This suggests that sex-related risk factors might moderate C9orf72 and GRN mediated phenotypic expression.

In a series of 2,094 outpatients with AD or FTD and followed at the Neurogenetic Regional Centre in southern Italy, women are about 2/3 of all the patients with dementia. There are no substantial gender differences in early-onset forms of AD and FTD and this is probably due to a greater weight of the genetics. Women are over-represented in late onset dementia and this effect is present independently from the type of dementia (AD and FTD), but AD has certainly a greater gender specificity compared to FTD (personal data, manuscript in preparation).

Thus, we can conclude that dementia phenotypes are gender related but one of the main questions is why and on which basis do the differences emerge.

Some possible fields such as different connections, different hormonal backgrounds, different genetics (or different expression of genes), different load of risk factors, can be further investigated for explanations.

Gender differences in behavioural and cognitive functioning are widely established in the current scientific literature. Biological and genetic differences in combination with environment and culture have resulted in the cognitive and behavioural differences among men and women. Different hormonal backgrounds, among the biological factors, may play some role mediating these differences also in the different brain connections.

The brain can be considered as a large-scale network of interconnected nodes within the human connectome. Small world network models could be relevant for understanding the emergence of complex behaviours and the resilience of brain systems to pathological attacks by diseases or other aberrant developments<sup>8</sup>.

Gender differences in the brain connectome may provide an important foundation to delineate the pathophysiological mechanisms underlying sex differences in neuropsychiatric disorders and to potentially guide the development of sex specific treatments.

A study based on a very large population of 949 youths (8-22 y, 428 males and 521 females) using the diffusion-based structural connectome of the brain, identified novel sex differences. The results established that male brains are optimized for intra-hemispheric communication and facilitate connectivity between perception and coordinated action whereas female brains, optimizing interhemispheric communication, facilitate communication between analytical and intuitive processing modes<sup>9</sup>. This happens in the physiological domain.

Considering the AD related risk, Mosconi<sup>10</sup>, studying amyloid positron emission tomography (PET) and fluorodeoxyglucose (FDG) PET, found a progressively increasing risk of AD in women undergoing menopausal changes. This suggests that endocrine aging accelerates chronologic aging in the female brain for several years, if not decades, prior to any emergence of possible clinical symptoms of AD.

Approximately 650 genes (14% of all genes in mouse tissue) are differentially expressed in the brains of males and females. The morphology of the brain may be sexually differentiated because of epigenetic mechanisms<sup>11-12</sup>.

Gene expression profiles have revealed substantial differences in the trajectory of aging changes between female and male brains. In female brains, 44.2% of genes were significantly changed from 6 months to 9 months and two-thirds showed downregulation. In contrast, in male brains, only 5.4% changed in the same period. This means that female and male brains follow profoundly dissimilar trajectories as they age; female brains undergo age-related changes much earlier than male brains; early changes in female brains signal the onset of a hypometabolic phenotype at risk for AD. These findings provide a mechanistic rationale for female susceptibility to AD and suggest a potential window of opportunity for AD prevention and risk reduction in women<sup>13</sup>.

Also sex-specific differences in neuro-mediators have been identified in male and female brains: they are neurochemically distinct concerning dopaminergic, serotonergic, and gamma-aminobutyric acid (GABA) ergic markers and serotonin is sexually differentiated at multiple levels<sup>14</sup>.

Although it is known that midlife hypertension was more common in men, it was, however, associated with

dementia risk only in women. A recent paper found that mid-adulthood hypertension was significantly associated with 65% of the increased dementia risk among women but not men. Onset of hypertension in mid-adulthood predicted 73% higher dementia risk in women (95% CI 1.24-2.40) compared to stable normotensive<sup>15</sup>.

In a doctoral thesis<sup>16</sup> studying a population of 1,925 AD patients, women present with a significantly higher load of risk factors (cholesterol, thyroid, hypertension and psychiatric disturbances).

ApoE4 strongly promotes amyloid- $\beta$  deposition in the brain<sup>17-19</sup> and the APOE4 effect is more pronounced in women than in men.

## Conclusion

The gender differences observed in dementias (by type, symptoms and phenotypic expression) seem to originate from the profound cerebral differences (genetic, hormonal and of connections) that exist between the two sexes. Much more research work, however, is needed because results are still at an early stage and have to be further inquired into for all types of dementia (also when rare), further checked and verified in different geographic areas all around the world. Furthermore, if gender specificity of dementing illnesses is to be confirmed, it will also be necessary to better understand whether different pathogenic pathways exist and based on this, possible future, gender related treatments.

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