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Actualities of disproportionate affection of women vs men in Alzheimer's disease

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Abstract

Background: Alzheimer's disease (AD) is a neurodegenerative disease of the elderly, being recognized worldwide as the most common cause of dementia. However, the harm generated by this disease to women and men is disproportionate, in women the disease is recorded twice as much. Numerous research studies have tried to find an answer regarding the causes of this disproportionality. So far, some fundamental differences between macroscopic, microscopic and biochemical structures of female vs. male brain have been investigated. First of all, emphasis was placed on macroscopic structural differences. In this study, a particular role was attributed to APOE4 gene which was shown to be an increased risk factor of AD in women who possess this allele. Hormonal changes in women, such as decreased postmenopausal estrogen, greatly influence disease incidence and prevalence. All these factors tell about the increased susceptibility of women to this disease. However, the definite mechanisms of this disease are incompletely elucidated and further studies are needed.
Conclusions: The identification of pathobiochemical mechanisms based on gender, that influence the incidence and prevalence of Alzheimer's disease is essential. Thus, it could be a target in the development of effective preventive therapeutic strategies from the prodromal phase of the disease. In this context, the development of personalized treatment according to gender specifics should be considered in future.
Key words: Alzheimer's disease, women, APOE4 gene, mitochondria, oestrogen, depression.

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Introduction

Dementia is a clinical syndrome characterized by a progressive and irreversible cognitive decline, which mainly affects the memory, functionality and person's behaviour, producing major personality changes. Alzheimer's disease (AD) is recognized as the most common cause of dementia worldwide, accounting for approximately 80% of all dementia cases [1].

Research study has shown that the diagnosis of Alzheimer's disease is defined by the presence of amyloid beta (Aβ), neurofibrillary glands (NFTs), neurodegeneration and not by the presence of specific symptomatology [2].

Statistics has shown that women are more affected by AD compared with men. In the United States, 2/3 of those affected by AD are women [3]. Initially, female longevity was considered the main reason of AD. Although, subsequent studies proved that the involved mechanisms are much more complex and include intrinsic factors related to genetic, endocrine, inflammatory, and structural characteristics of the brain. All these factors have a well-defined role in this imbalance. [4].

Brain structural differences

First and foremost, women's and men's brains differ structurally. In various studies, with the help of MRI, was shown that men have larger tonsil and thalamus, while women have a larger hippocampus [5]. Women's cerebral volume is smaller, but richer in grey matter as compared with men's one, which is larger in size and has bigger volume of white matter [6]. As well, men have greater interhemispheric connectivity. However, when we talk about metabolism, in women the blood flow is more abundant in the parietal cortex, and in men it is richer in motor, visual cortex, and in cerebellum [7, 8].

Implications of APOE4 gene

APOE gene encodes APOE protein, which binds to lipids, forming lipoproteins. Their role is essential in the cholesterol transport through the blood stream [9]. At least 3 alleles of APOE gene are known: APOE2, APOE3 and APOE4 [10]. ε4 allele of APOE4 gene represents a genetic risk factor for sporadic AD with late onset [11]. APOE4 allele was associated with mitochondrial dysfunction and glucose hypometabolism in the brain [12]. There are major differences between female and male APOE4 allele carriers. Women who possess E4 allele have a higher genetic risk of AD developing, which is manifested by a more rapid evolution with a more severe cognitive decline, compared with men that have the same allele [10, 13]. Concurrently, the female E4 allele carriers are more likely to develop AD because they are more susceptible to protein accumulation. This condition effects directly beta amyloid aggregation and promotes pro-

teolytic cleavage that generates toxic fragments in the brain [6, 14]. Women are endowed with a larger neural network that serves as brain reserve and allows the compensation of amyloid deposition, that results in a significantly higher verbal memory [15].

Hormonal imbalance and menopause

AD pathobiochemical changes manifest slowly, progressively and may last for decades. Studies suggest that the increased risk for women to develop the disease between 65 and 75 years is due to hormonal changes and menopause, which begin 15-20 years earlier [16]. Menopause is considered to be a neuroendocrine transition and ends with reproductive senescence. It presents a set of neurological symptoms, and causes estrogen regulation dysfunctions, such as thermoregulation, sleep and circadian rhythms, depression and impairment of multiple cognitive domains. It has been shown that the menopause onset is directly influenced by the uncoupling of brain energy metabolism, which in turn is mediated by estrogen. Both men and women produce estrogen, only that women produce a much higher amount of estrogen, which is also called the female hormone. With menopause onset, hormone production decreases. On the other hand, men continue to produce testosterone – the male sex hormone, which when reaches the brain cells, is converted into estrogen. In conclusion, at the same age, women have less estrogen in the brain compared with men [17, 18].

Oestrogen actions in the brain

Oestrogen plays an essential role and has multiple functions in the reproductive, cardiovascular, skeletal, and central nervous systems physiology. Oestrogen is vital for prefrontal cortex and hippocampus functioning and initiates spinogenesis and synaptogenesis [19, 20]. Three physiological estrogens are known, including estradiol (E2). During menopause, it decreases producing a series of changes in cognition, sleep, and mood. Studies have shown that estradiol also interacts with cholinergic, dopaminergic and mitochondrial functions [21]. Oestrogen has a neuroprotective role against dementia, and its dysfunction aggravates the neurodegenerative process, especially in women [22, 23]. For many years, epidemiological studies have shown that the prevalence of Alzheimer's disease was significantly lower in women taking postmenopausal hormone therapy, or the disease was milder compared with those who did not [24]. However, a case-control study in Finland, conducted between 1999-2013 and attended by 84739 women diagnosed with postmenopausal AD, has shown surprizing results. The results of the study demonstrated that long-term systemic hormone therapy may be accompanied by an increased risk of AD. Only vaginal estradiol presents no risk [25].

Mitochondria

In cellular metabolism, mitochondria play an essential role, not only for ATP production, but also in the production of reactive oxygen species (ROS) following the discharge of electrons from the respiratory chain [26]. In the presence of beta amyloid, mitochondria increase the formation of reactive oxygen species which on the one hand are harmful, but on the other hand act as signalling molecules [27]. Mitochondria are an essential source of ROS in cells that have high oxidative capacity, such as neurons, skeletal muscle cells and cardiomyocytes. Upon prolonged exposure, ROS can produce mutations in mtDNA, which accumulate over years. Primordial impairment occurs on the mitochondrial cells of the brain. However, in mouse experiments, in the mitochondrial cells of the female mouse brain, lower oxidative stress was found when compared with the male ones [28]. The liver and brain mitochondria of the female mouse produce less peroxides than the male ones. Nevertheless, ovarectomy reversed this process, equalling female/male peroxides production. Estrogen replacement therapy produced surprising results, namely the peroxides production was smaller in female than in male (F<M). Thus, the lack of postmenopausal oestrogen administration may be the reason for the increased AD prevalence among women [29].

Depression prevalence in women

Depression is an important risk factor for developing Alzheimer's disease [30]. The hippocampus represents a brain structure composed of dentate gyrus, and hippocampus itself which is composed of three fields – CA1, CA2, CA3 and subiculum. It is a structure responsible for learning and memory, which is affected in AD [31]. Gender and sex differences exist and are related mainly to hippocampal plasticity and cognition, women being more prone to cognitive decline in Alzheimer's disease [32]. Numerous studies have shown that the increased prevalence of depression in women correlates with hormonal changes and is predominantly manifested during puberty, before menstruation, after pregnancy and perimenopause. Estrogen administration decreases the risk of depression. But why do men who possess testosterone have lower rates of depression? Research has shown that in the male brain there are many receptors for estrogen, and through endogenous aromatase, testosterone turns into estrogen. Apart from the hormonal implications, the presence of different brain circuits in men is suspected [33]. In women with mild cognitive impairment, proteins spread earlier and faster through the brain than in men's brain [34, 35].

Conclusions

Gender in Alzheimer's disease could be a potential risk factor, as studies have shown that 2/3 of women are affected by this disease. Although, it was initially thought that this is due to the female longevity. Later, various research studies have shown the involvement of several macroscopic and biochemical factors in this disproportionality.

The identification of pathobiochemical mechanisms based on gender, that influence the incidence and prevalence of Alzheimer's disease is essential. Thus, it could be a target in the development of effective preventive therapeutic strategies from the prodromal phase of the disease. In this context, the development of personalized treatment according to gender specifics should be considered in future.

References

1. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res. 2018;7. pii: F1000 Faculty Rev-1161.
2. Jack CR Jr, Therneau TM, Weigand SD, Wiste HJ, et al. Prevalence of biologically vs clinically defined Alzheimer spectrum entities using the National Institute on Aging–Alzheimer's Association research framework. JAMA Neurol. 2019;76(10):1174-1183.
3. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. Alzheimer's Dement. 2018;14(9):1171-1183.
4. Fisher DW, Bennett DA, Dong H. Sexual dimorphism in predisposition to Alzheimer's disease. Neurobiol Aging. 2018;70:308-324.
5. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. Front Neuroendocrinol. 2014;35(3):385-403.
6. Toro CA, Zhang L, Cao J, Cai D. Sex differences in Alzheimer's disease: understanding the molecular impact. Brain Res. 2019;1719:194-207. doi: 10.1016/j.brainres.2019.05.031.
7. Ingalhalikar M, Smith A, Parker D, Satterthwaite TD, Elliott MA, Ruparel K, Hakonarson H, Gur RE, Gur RC, Verma R. Sex differences in the structural connectome of the human brain. Proc Natl Acad Sci USA. 2014;111(2):823-828.
8. Hsieh TC, Lin WY, Ding HJ, Sun SS, et al. Sex- and age-related differences in brain FDG metabolism of healthy adults: an SPM analysis. J Neuroimaging. 2011;22(1):21-7.
9. Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer's disease and other dementias. Dialogues Clin Neurosci. 2016;18(4):437-446.
10. Hsu M, Dedhia M, Crusio WE, Delprato A. Sex differences in gene expression patterns associated with the *APOE4* allele. F1000Res. 2019;8:387.
11. Ungar L, Altmann A, Greicius MD. Apolipoprotein E, gender and Alzheimer's disease: an overlooked, but potent and promising interaction. Brain Imaging Behav. 2014;8(2):262-273.
12. Wang Y, Brinton RD. Triad of risk for late onset Alzheimer's disease: mitochondrial haplotype, APOE genotype and chromosomal sex. Front Aging Neurosci. 2016;8:232.
13. Mazure CM, Swendsen J. Sex differences in Alzheimer's disease and other dementias. Lancet Neurol. 2016;15(5):451-452.
14. Paranjpe M, Liu M, Paranjpe I, Wang R, Benzinger T, Zhou Y. Sex modulates the ApoE ε4 effect on tau ^{18}F-AV-1451 PET imaging in individuals with normal aging and mild cognitive impairment. J Nucl Med. 2019;60(Suppl 1):253.
15. Sundermann EE, Tran M, Maki PM, Bondi MW. Sex differences in the association between apolipoprotein E ε4 allele and Alzheimer's disease markers. Alzheimer's Dement (Amst). 2018;10:438-447.
16. Patel M. Revising the risk of Alzheimer's disease in women. Nat Rev Neurol. 2017;13(10):575.
17. Scheyer O, Rahman A, Hristov H, Berkowitz C, Isaacson RS, Diaz Brinton R, Mosconi L. Female sex and Alzheimer's risk: the menopause connection. J Prev Alzheimers Dis. 2018;5(4)18. Alzheimer's Society (UK). Hormones and dementia [Internet]. London: The Society; 2020 [cited 2020 Feb 18]. Available from: https://www.alzheimers.org.uk/about-dementia/risk-factors-and-prevention/hormones-and-dementia
19. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev. 2013;34(3):309-338.
20. Hara Y, Waters EM, McEwen BS, Morrison JH. Estrogen effects on cognitive and synaptic health over the lifecourse. Physiol Rev. 2015;95(3):785-807.
21. Russell JK, Jones CK, Newhouse PA. The role of estrogen in brain and cognitive aging. Neurotherapeutics. 2019 Jul;16(3):649-665.
22. Rahman A, Jackson H, Hristov H, Isaacson RS, Saif N, Shetty T, et al. Sex and gender driven modifiers of Alzheimer's disease: the role for estrogenic control across age, race, medical, and lifestyle risks. Front Aging Neurosci. 2019;11:315.
23. Tenkorang MA, Snyder B, Cunningham RL. Sex-related differences in oxidative stress and neurodegeneration. Steroids. 2018;133:21-27.
24. Cutter WJ, Norbury R, Murphy DG. Oestrogen, brain function, and neuropsychiatric disorders. J Neurol Neurosurg Psychiatry. 2003;74:837-840.
25. Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O, Mikkola TS. Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. BMJ. 2019;364:l665.
26. Farhat F, Amérand A, Simon B, Guegueniat N, Moisan C. Gender-dependent differences of mitochondrial function and oxidative stress in rat skeletal muscle at rest and after exercise training. Redox Rep. 2017;22(6):508-514.
27. Viña J, Lloret A, Vallés SL, Borrás C, Badía MC, Pallardó FV, Sastre J, Alonso MD. Effect of gender on mitochondrial toxicity of Alzheimer's Abeta peptide. Antioxid Redox Signal. 2007;9(10):1677-1690.
28. Ventura-Clapier R, Moulin M, Piguereau J, Lemaire C, et al. Mitochondria: a central target for sex differences in pathologies. Clin Sci (Lond). 2017;131(9):803-822 .
29. Vina J, Lloret A. Why women have more Alzheimer's disease than men: gender and mitochondrial toxicity of amyloid-β peptide. J Alzheimer's Dis. 2010;20 Suppl 2:S527-S533.
30. Underwood EA, Davidson HP, Azam AB, Tierney MC. Sex differences in depression as a risk factor for Alzheimer's disease: a systematic review. Innov Aging. 2019;3(2):igz015.
31. Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol Neurodegener. 2011;6:85.
32. Yagi S, Galea LAM. Sex differences in hippocampal cognition and neurogenesis. Neuropsychopharmacology. 2019;44(1):200-213.
33. Albert PR. Why is depression more prevalent in women? J Psychiatry Neurosci. 2015;40(4):219-221.
34. Fisher Center for Alzheimer's Research Foundation. Why more women than men have Alzheimer's disease [Internet]. New York: The Center; 2020 [cited 2020 Feb 18]. Available from: https://www.alzinfo.org/articles/research/why-more-women-than-men-have-alzheimers-disease/
35. Buckley RF, Mormino EC, Rabin JS, Hohman TJ, Landau S, Hanseeuw BJ, Jacobs HIL, et al. Sex differences in the association of global amyloid and regional tau deposition measured by positron emission tomography in clinically normal older adults. JAMA Neurol. 2019;76(5):542-551.

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Authors' contributions

AO designed the trial and drafted the first manuscript; LL interpreted the data and revised the manuscript critically. Both authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate

No approval was required for this review study.

Conflict of Interests

No competing interests were disclosed.