

## 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 (A $\beta$ ), neurofibrillary tangles (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 inter-hemispheric 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].  $\epsilon$ 4 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 pre-frontal 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 surprising 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, ovariectomy 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.

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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.