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Reproductive Markers in Alzheimer's Disease Progression: A Mini Review

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ABSTRACT

Accumulating evidence suggests that reproductive markers, such as age at menarche, are associated with cognitive function and the risk of developing Alzheimer's disease (AD). These reproductive markers offer promising potential for predicting the risk of AD, underscoring the necessity for sex-specific considerations in understanding and managing this neurodegenerative disorder. This review first discusses recent findings on reproductive markers in AD progression, and further points out the direction for future research to unravel the complex interplay between reproductive health and cognitive health. We advocate for the incorporation of sex heterogeneity into AD precision medicine to tailor sex-specific diagnostic and intervention approaches.

Introduction

Alzheimer's disease (AD) represents a neurodegenerative condition characterized by a progressively worsening symptoms and clinical stages, paralleled by the accumulation of pathological AD biomarkers[1]. With the aging global population, the prevalence of AD is set to rise, presenting a substantial societal challenge[2]. However, currently, the effective treatment for AD is limited. In this context, identifying risk factors during the preclinical stages, which may aid early detection, emerges as the most promising strategy for combating AD. Sex stands out as a pivotal factor in precision medicine, emphasizing the importance of creating tailored diagnostic tools, interventions, and therapeutic approaches separately for men and women. Consequently, a deep understanding of sex differences is important. Many studies have demonstrated that women face a greater risk of developing AD over their lifetime compared to men[3-5]. Sex differences have been investigated in neuropsychological test[6,7], blood-based biomarkers[8,9], early-life (i.e., education[8]) and later-life pathological (i.e., beta-amyloid[10]) factors. Reproductive markers, which are biological signals or indicators tied to the developmental stage reproductive system, play a crucial role in the observed sex disparities[11]. Thus, it becomes important to explore the relationship between reproductive markers and AD to further elucidate the sex differences in the pathogenicity of AD.

In our prior research, we examined how various reproductive markers, such as the age of menarche and menopause, and the incident of AD as well as the rate of cognitive decline among women aged 60

and above. This used the data from the community-based, longitudinal Framingham Heart Study Offspring cohort[12]. Others have also investigated the associations of cognitive health with reproductive history (parity, age at first pregnancy, breastfeeding)[13], menstrual cycle[14], and sex hormone markers[15] in various cohorts. This review discusses available findings in the field regarding the impact of reproductive markers on AD and cognitive function. We also outline four research directions for future investigation on the role of sex differences in AD.

Ages at Menarche and Menopause and AD

The age of menarche marks a critical point in the onset of puberty for women[16], influenced by the combination of genetic[17] and environmental[18] factors. There is mixed evidence regarding the impact of early menarche on cognitive decline in later life. Previous study suggests that earlier menarche may be associated with better cognitive performance in later life[19], potentially due to prolonged exposure to estrogen. However, other research indicates no significant relationship between age of menarche and global cognitive decline[20], suggesting that the effects of early menarche on cognitive health may be complex. Furthermore, the accuracy of findings reliant on self-reported reproductive history may be compromised by recall bias, highlighting the need for caution in interpreting these findings.

Menopause, defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity, marks a significant transition in a woman's reproductive life[21]. The timing of this event can vary widely among individuals, influenced by both genetics and lifestyle factors[22,23]. Women who experience menopause at an earlier age (e.g., before 45) have been found to be at a potentially higher risk for dementia[24]. Early cessation of ovarian function leads to a decrease in estrogen levels, a hormone that has been hypothesized to play a protective role against cognitive decline[25]. Therefore, reduced lifetime exposure to estrogen could contribute to an increased vulnerability to AD. An earlier onset of menopause has been associated with a higher risk for cardiovascular diseases and stroke, potentially offering another route through which cognitive impairment can occur[26].

Sex Hormone Markers and AD

Sex hormones have been recognized for their neuroprotective, anti-inflammatory, and antioxidant properties[15,27]. These properties affect AD risk and progression differently across sexes. While AD progresses faster in men, women tend to experience more severe manifestations of the disease[28,29]. This discrepancy is likely due to variations in neurophysiological substrates and the differential effects of hormones across genders[28,29]. In women, hormonal fluctuations during events such as pregnancy also impact hormonal levels[30]. Estrogens influence cognition by enhancing synaptic formation and neurotransmitter systems[31]. Human trials with estrogen-containing hormone therapies yield mixed results[32]. In men, age-related decline in estrogen may negatively affect cognition, especially in younger individuals[32,33]. However, research findings are inconsistent due to limited sample sizes of these previous studies and challenges in disentangling estrogen's effects from those of androgens, and the gradual estrogen-level decline in men compared to women[32,33]. Overall, the impact of estrogen on men's cognition remains less clear compared to women[11,33]. Moreover, the dynamics of hormones are critical, not just the levels of specific hormones like estrogen or testosterone. These dynamics involve fluctuations in hormone levels, receptor sensitivity, and interactions among various hormones, which collectively influence AD risk and progression. This complex interaction suggests that a broader perspective on hormone dynamics is essential for understanding their full impact on AD.

Elevated levels of estrogen and testosterone decrease amyloid-β (Aβ) production by regulating the amyloid precursor protein (APP) proteolytic process[29]. Both hormones increase the secretion of β-APPs while reducing Aβ production through non-amyloidogenic processing pathways activated by mitogen-activated protein kinase and androgen receptor signaling[29]. Testosterone exhibits stronger effects than estrogen in decreasing β-APP secretion, while estrogen enhances Aβ breakdown and excretion by upregulating Aβ-degrading enzymes such as neprilysin[28]. Reduced estradiol (E2) levels are linked to a higher risk of AD in women demonstrated by accelerated AD-like pathology in experimental rodent studies[30]. Reduced estrogen exposure in adulthood has been shown to increase AD risk in women suggesting that lower estrogen levels may heighten susceptibility to AD[29]. However, clinical trials on estrogen-based hormone therapy yield conflicting results, indicating uncertainty about its therapeutic effectiveness[29,34]. Normal age-related loss of testosterone significantly increases the risk of AD in men. Studies consistently reported lower levels of total testosterone in men with AD, suggesting reduced testosterone levels may promote the development of AD in men, as evident in both clinical and rodent studies[34,35]. Analysis of longitudinal data indicates that low serum testosterone precedes AD diagnosis by at least 10 years[34]. Higher free testosterone levels are linked to lower cerebral Aβ deposition and cognitive impairment in older subjects, while low levels are associated with increased Aβ deposition and synaptic dysfunction, exacerbating cognitive decline[34,35]. Limited research on androgen replacement therapy suggests potential cognitive benefits, such as improved memory and quality of life, in older men[29]. However, current clinical trials assessing the effect of testosterone supplementation

on cognitive function in older men have not yet reached a conclusive result[36]. Decreased sex hormone levels, particularly estradiol (E2), are linked to heightened inflammation observed in hypogonadal men, aged men, and post-menopausal women[29,30]. Reduced E2 production during menopause and perimenopause may contribute to the pro-inflammatory profile in aging women's brains, potentially increasing the risk of neurological disorders like AD[28,29,33]. Testosterone also exhibits anti-inflammatory effects, with decreased levels associated with altered inflammatory responses[29,34]. Both E2 and testosterone can modulate neuroinflammation, indicating a role in regulating neurodegenerative disease progression[29,33,35].

Future Directions

Multi Cohort Study

Current research predominantly focuses on data from single cohort studies, which typically feature limited population diversity. This can restrict the ability to fully capture the variability in disease progression across different demographic groups, potentially leading to inconsistent findings. To address this and effectively synthesize diverse findings, it is essential to use a variety of multi-cohort analytic techniques[37]. These methods enhance the robustness and comprehensiveness of the research by integrating data from various cohorts, broadening the scope and applicability of the findings. Utilizing a multicohort study to investigate the relationship between reproductive markers and AD offers several advantages. First, it enables researchers to draw from a diverse population base, enhancing the generalizability of the findings. By comparing data across different cohorts, it becomes possible to identify consistent patterns and associations, thereby strengthening the evidence for any observed links. Additionally, multicohort studies can provide a broader range of data on genetic, environmental, and lifestyle factors, allowing for a more comprehensive analysis of how these variables interact with reproductive markers to influence AD risk. There is a range of multi-cohort analytic approaches that could be used, such as pooled data analysis and meta-analysis[37]. These methods will help in consolidating data and deriving more robust and validated conclusions.

More Comprehensive Data

Recognizing sex as a significant risk factor for AD requires a deeper investigation into how it intersects with genetic, health, and lifestyle factors to influence the disease's progression. Previous research has indicated that early life factors, such as education[8], play a role in the potential sex differences observed in the incidence of AD, prompting a deeper exploration of the nature versus nurture debate. Previous study also found sex difference in genetic and lifestyle factors for AD[38]. Future research should aim for a more comprehensive collection and thorough analysis of data that accounts for these multifaceted interactions. Specifically, there is a critical need to explore the roles of vascular health, inflammation, and neuroprotection in the context of AD, with a particular focus on how these mechanisms are modulated by sex hormones. Given the pivotal role of sex hormones in these processes, it is also essential to examine how fluctuations in hormone levels across different life stages, particularly in women, may impact the risk and progression of AD. This includes studying the effects of menopause and the potential protective benefits of hormone replacement therapy at various stages of disease development. Especially, with the advancement of digital technology, the continuous collection of vital health indicators, such as sleep and physical activity measures, has become feasible. An increasing number of studies have identified new data modalities associated with cognitive impairments and capable of detecting early and subtle cognitive changes, such as voice analysis[39,40] and digital neuropsychological assessments[41] such as the digital clock drawing test[42]. Exploring the sex differences in these novel data modalities and their interactions with reproductive markers holds broad prospects.

Existing research has demonstrated that constructing separate machine learning models for men and women in neuropsychological testing can enhance diagnostic performance[6]. Therefore, by utilizing the enriched dataset, future efforts can focus on designing diagnostic and therapeutic tools that are tailored to sex differences. This approach could lead to improved treatment outcomes in AD precision medicine and deepen our understanding of AD progression across men and women.

Genetics and Genomics Study

Previous studies have shown the association between genomic variations and ages at menarche and menopause[43,44], as well as the role of genetic factors in predicting AD[45,46]. However, the verification of common genetic variants associated with the ages at menarche and menopause and AD risk across different ethnic groups remains an area requiring additional exploration[47]. The intersection of genetics and genomics with reproductive markers presents a promising avenue for understanding the disease's progression.

Causal Analysis

To date, observational studies have revealed a diverse range of outcomes in the link between hormonal markers and AD risk[29,48]. Consequently, future research should aim to clarify whether the relationship between endogenous estrogen exposure and AD susceptibility is causal or if this association

can be fully explained by other unmeasured confounders. Mendelian randomization studies, employing genetic variants like single-nucleotide polymorphisms as instrumental variables for known risk factors, have become a prevalent method for assessing the causal impact of an exposure on a specific outcome[49,50]. In the future, this methodology could be applied to perform genetic and genomic investigations into sex difference observed in AD, aiming to uncover the causal connections between reproductive markers and AD, as well as changes in cognitive function.

Conclusions

The exact mechanisms linking reproductive markers to AD progression remain elusive. This review not only highlights the importance of considering sex differences in AD research but also points a path forward for future investigations. By focusing on the complex relationships between reproductive markers and AD, we can pave the way for more personalized and effective strategies for combating this disease.

Conflict of Interest

R.A. is a scientific advisor to Signant Health and NovoNordisk, and a consultant to the Davos Alzheimer's Collaborative. PMD has received research grants, advisory/board fees and/or stock from several companies and is a co-inventor on several patents related to the diagnosis and treatment of dementia. Other authors declare that they have no conflict of interests.

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